HOU | 2009 VOL 2 | ISSUE 4

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

- Identify patients with hematologic cancer who may be eligible for full- or reduced-intensity stem cell transplant.
- Counsel patients with hematologic cancer about the incidence and management of side effects and toxicities associated with various systemic therapies.
- Tailor up-front/induction therapy based on individual and disease characteristics for patients with multiple myeloma.
- Develop evidence-based treatment algorithms for frequently encountered adult acute and chronic leukemias.
- Educate patients with indolent or aggressive B-cell lymphomas about the benefits and risks of induction, consolidation and/or maintenance treatment strategies.
- Summarize emerging data with novel agents and combinations in the setting of newly diagnosed or relapsed/refractory B- and T-cell non-Hodgkin lymphomas.
- Use cytogenetics to individualize the clinical management of multiple myeloma, myelodysplastic syndrome and acute or chronic leukemia.
- Recall the efficacy and side effects of hypomethylating and immunomodulating agents in the treatment of higher-risk myelodysplastic syndrome.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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This program is supported by educational grants from Celgene Corporation, Cephalon Inc, Eisai Inc, Genentech BioOncology/Biogen Idec, Genzyme Corporation, GlaxoSmithKline and Millennium Pharmaceuticals Inc.

Last review date: November 2009; Release date: November 2009; Expiration date: November 2010

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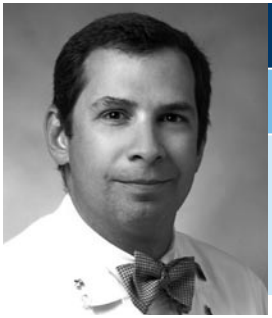


INTERVIEW

Sergio Giralt, MD

Dr Giralt is Professor of Medicine of Stem Cell Transplantation and Lymphoma/Myeloma and Deputy Chair of Stem Cell Transplantation at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-10

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: What factors influence your choice of induction therapy for patients with multiple myeloma?

DR GIRALT: Twenty years ago, it was relatively easy to treat myeloma because only two types of treatment existed. We now have a variety of treatments and need to tailor the treatment to each patient.

Certain factors must be considered for patients with high tumor burden, particularly those in whom renal function is at risk. You want to control the disease quickly.

Pulse dexamethasone probably remains the most effective single agent despite its associated toxicities. So for kidney preservation in a patient with high tumor burden, I believe that pulse dexamethasone should be the first line of

attack. You need to be careful using lenalidomide among patients with renal failure. For a patient with a high tumor mass and renal failure, the combination to consider is pulse dexamethasone/bortezomib with an alkylator.

You should not administer high-dose dexamethasone to patients with poor performance statuses, particularly those who are frail or elderly. The randomized trial ECOG-E4A03 with lenalidomide and low-dose versus high-dose dexamethasone suggests that patients don't fare well with the latter (Rajkumar 2009).

Another consideration with regard to treatment-specific toxicities if you are considering administering lenalidomide and thalidomide is that these are thrombogenic agents.

Consider whether the patient has a history of thrombogenesis. If a clot forms, could it mean disaster? What would you do for someone with four stents who is receiving clopidogrel bisulfate and aspirin? Would thalidomide or lenalidomide be the correct choice, or would you rather choose bortezomib? What would you do for someone with a history of a bleeding ulcer three months ago? Would you want to administer an anticoagulation agent?

What about a patient with severe diabetic neuropathy? This is a patient to whom you probably don't want to administer bortezomib or thalidomide. For patients with diabetes but without neuropathy, the issue of bortezomib versus thalidomide becomes whether or not they have adequate renal function.

Tracks 4-6

DR LOVE: One of our recent Patterns of Care surveys reported that not all patients with myeloma receive cytogenetic and FISH assays (1.1). Do situations exist in which you would not order these assays?

DR GIRALT: I believe that all academic centers are performing cytogenetic and FISH assays. But in discussions with community physicians, many of them ask me, "Why would I do this if it won't change my treatment approach? What difference does it make?"

We're at a watershed moment. Emerging data indicate that bortezomib may be associated with better outcomes for some cytogenetic abnormalities (Cavo 2008; San Miguel 2008).

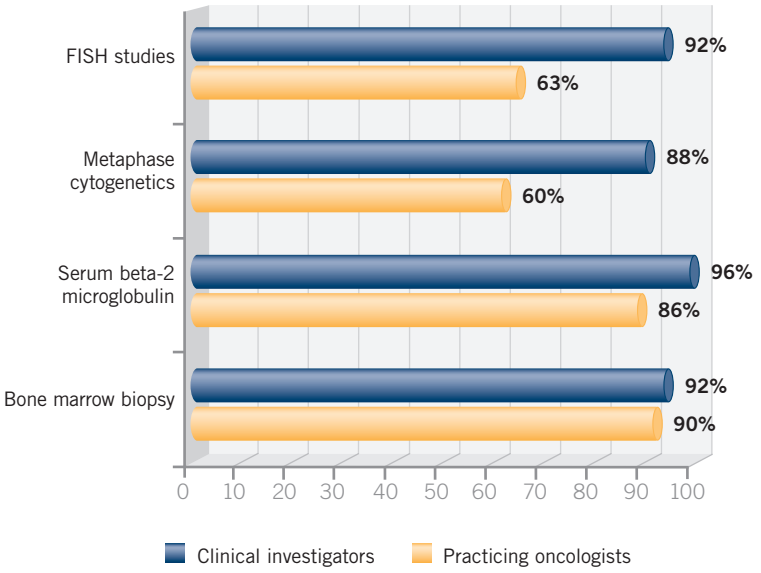
Until a direct comparison is made of bortezomib and lenalidomide as induction therapy, we won't know. Another issue for community oncologists is that many have trouble obtaining approval for lenalidomide as first-line therapy. Thus their first-line therapy choice is automatically bortezomib.

Controversy is emerging around the presence of adverse cytogenetic risk abnormalities, and the question is, based on data from the front-line studies, whether these imply the need for triple therapy — an immunomodulatory drug, a proteasome inhibitor and steroids — or at least the need for bortezomib.

I believe that patients with poor-risk cytogenetic abnormalities should be seriously considered for triple therapy with bortezomib/lenalidomide and dexamethasone (VRD).

Our goal is to achieve a complete remission. We believe that triple therapy with VRD, followed by transplant, is the minimum necessary treatment for 80 to 90 percent of patients.

1.1 **Which of the following do you consider a standard part of the workup for a 55-year-old patient with newly diagnosed multiple myeloma?**



SOURCE: Research To Practice. *Patterns of Care* Multiple Myeloma 2009;1(1). Available at: **www.ResearchToPractice.com/POCMM109**. Accessed October 21, 2009.

Track 8

DR LOVE: What induction regimen would you choose for a patient not eligible for subsequent transplant?

DR GIRALT: I'm not a strong proponent of melphalan/prednisone/thalidomide or melphalan/prednisone/bortezomib, so I'd administer the same type of induction for older and younger patients.

For older patients, I may use once-weekly bortezomib more on the basis of the lymphoma data (de Vos 2009). I increasingly use bortezomib once a week after the first two cycles. The lymphoma data are suggestive of less neuropathy with

once-a-week administration (de Vos 2009), but people familiar with myeloma would say, "Preexisting neuropathy occurs with lymphoma."

DR LOVE: What are your thoughts on the Palumbo data reported at ASCO 2009 in terms of less neuropathy with the weekly bortezomib infusion schedule (Palumbo 2009; [1.2])?

DR GIRALT: I'm beginning to see changes in the pattern of practice. Community oncologists are already adopting this approach. What struck people were the facts that these data involved a relatively large number of patients, they came from a reputable group and the response rates weren't affected.

When patients experience numbness or tingling after two or three cycles, instead of reducing the dose sometimes oncologists are administering bortezomib once a week. ■

1.2

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- or once-weekly bortezomib.

V = bortezomib; M = melphalan; P = prednisone; T = thalidomide

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

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De Vos S et al. **Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma.** *J Clin Oncol* 2009;27(30):5023-30.

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

Rajkumar SV et al. **Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial.** *Lancet Oncol* 2009;[Epub ahead of print].

San Miguel JF et al. **Updated follow-up and results of subsequent therapy in the Phase III VISTA trial: Bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma.** *Proc ASH* 2008;**Abstract 650**.

INTERVIEW

Julie M Vose, MD

Dr Vose is Neumann M and Mildred E Harris Professor, Chief of the Section of Hematology/Oncology and Professor of Medicine at Nebraska Medical Center in Omaha, Nebraska.

Tracks 1-23

Select Excerpts from the Interview

Track 1

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

DR VOSE: Several important drugs have recently been approved or are about to be approved, which will be helpful for physicians in practice. Bendamustine has been approved for CLL and indolent lymphoma. Although it has been available in Germany for many years, in the United States we're still learning how to use it and combine it with other agents. I believe that it will be useful in treating both diseases. It does cause some cytopenias, so it's probably better to use earlier in the course of the disease rather than later.

The dose on the package insert is 120 mg/m^2 for lymphoma and 100 mg/m^2 for CLL, administered on days one and two. I have found that this dose is too high, and most patients need it reduced immediately, so I start with 90 mg/m^2 on the same schedule, which is more tolerable. When we combine it with other agents, we sometimes need to reduce the dose even further.

DR LOVE: What agents are being combined with bendamustine in clinical trials?

DR VOSE: We participated in an interesting study evaluating the combination of bendamustine, bortezomib and rituximab for patients with indolent and mantle-cell lymphomas. The combination was shown to be active and fairly well tolerated. Bendamustine is active in the treatment of mantle-cell lymphoma. We wanted to evaluate it in combination with other agents for mantle-cell lymphoma and then decided to include indolent lymphoma.

2.1

Rituximab/Bendamustine (R-B) versus R-CHOP as First-Line Therapy for Follicular, Indolent or Mantle-Cell Lymphoma

Second interim analysis (median follow-up of 28 months)

Efficacy	R-B (n = 221)	R-CHOP (n = 212)
Overall response rate	94%	93%
Complete response rate	41%	33%
Median event-free survival	Not reached	39 months

Safety	R-B (n = 221)	R-CHOP (n = 212)
Alopecia	0%	89%
Any grade infection	25%	37%
Grade III/IV leukopenia	19%	36%

SOURCE: Rummel MJ et al. *Proc ASH* 2008;**Abstract 2596**.

Bortezomib does have activity in some indolent lymphomas, but it's only 10 or 15 percent, which is why it made more sense to study it in combination.

As for rituximab, a randomized study conducted in Europe compared bendamustine/rituximab to R-CHOP for patients with indolent lymphomas. Although the response rates were similar between the two arms, the patients who received bendamustine/rituximab experienced less toxicity, specifically with regard to alopecia and infectious complications (Rummel 2008; [2.1]). This combination might be an excellent alternative for elderly patients or patients for whom we're concerned about cardiotoxicity.

Track 5

DR LOVE: How does ofatumumab compare to rituximab?

DR VOSE: Ofatumumab is a fully humanized anti-CD20 monoclonal antibody, whereas rituximab is chimeric and attacks a different epitope. Ofatumumab has slightly different characteristics than rituximab regarding complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. Also, ofatumumab appears to work for patients who have lower CD20 levels on the surface of their lymphomas. Therefore, it should be more effective than rituximab in treating CLL. Rituximab alone doesn't work well for CLL because of low CD20 levels. A clinical trial was reported at ASCO that evaluated ofatumumab for patients with fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory CLL, some of whom had previously received rituximab. In that study, ofatumumab exhibited good activity with modest side effects, and the patients tolerated it fairly well (Wierda 2009; [2.2]). (Editor's note: On October 26, 2009, after this interview was conducted, the FDA approved ofatumumab for the treatment of CLL refractory to fludarabine and alemtuzumab).

2.2

Activity of Ofatumumab in Patients with Fludarabine- and Alemtuzumab-Refractory or Bulky Fludarabine-Refractory CLL: Efficacy Outcomes by Rituximab Exposure

	Fludarabine- and alemtuzumab-refractory (n = 59)			Bulky fludarabine-refractory (n = 79)		
	N	ORR	Median PFS	N	ORR	Median PFS
Any prior R	35	54%	5.5 months	43	44%	5.5 months
FR	18	50%	5.5 months	27	52%	5.6 months
FRC	16	50%	4.6 months	16	44%	5.6 months
No prior R	24	63%	7.1 months	36	50%	6.4 months

N = number of patients; ORR = overall response rate; PFS = progression-free survival; R = rituximab; F = fludarabine; C = cyclophosphamide

SOURCE: Wierda WG et al. *Proc ASCO* 2009;**Abstract 7044**.

Track 8

DR LOVE: Would you review the efficacy of lenalidomide in the treatment of lymphoma?

DR VOSE: Lenalidomide is an interesting agent that has several different mechanisms of action, all of which we don't understand. It probably helps with the microenvironment, changing the cytokine profile and angiogenesis.

In a large, broad trial, the lymphoma with the highest response rate to lenalidomide appeared to be mantle-cell lymphoma, with approximately a 40 percent response rate (Zinzani 2008). Lenalidomide is tolerated well, with mild cytopenias, and it is a useful agent for these patients.

At ASCO we presented data from an international Phase II trial, NHL-003, evaluating lenalidomide monotherapy for patients with relapsed or refractory diffuse large B-cell lymphoma. The overall response rate was approximately 30 percent (Czuczman 2009; [2.3]).

In other indolent lymphomas it has a low level of activity, perhaps in the range of 10 to 20 percent. ■

2.3

Efficacy and Safety of Lenalidomide Oral Monotherapy for Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Efficacy data	N	CR/CRu	PR	ORR
No history of stem cell transplant	103	7%	23%	30%
History of stem cell transplant	46	11%	20%	30%

Grade III or IV adverse events occurring in more than five percent of patients

Neutropenia	34%	Thrombocytopenia	18%

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

SOURCE: Czuczman MS et al. *Proc ASCO* 2009;**Abstract e19504**.

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Czuczman MS et al. **Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma: Results from an international study (NHL-003).** *Proc ASCO* 2009;**Abstract e19504**.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: Results of a randomized phase III study of the Study Group Indolent Lymphomas (StiL).** *Proc ASH* 2008;**Abstract 2596**.

Wierda WG et al. **Activity of ofatumumab, a novel CD20 mAb, and prior rituximab exposure in patients with fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory chronic lymphocytic leukemia (CLL).** *Proc ASCO* 2009;**Abstract 7044**.

Zinzani PL et al. **Confirmation of the efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results of an international study (NHL-003).** *Proc ASH* 2008;**Abstract 262**.

INTERVIEW

Allen SR Yang, MD, PhD

Dr Yang is Assistant Professor of Medicine at the University of Southern California in Los Angeles, California.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: What did you think of the data from the AZA-001 trial of azacitidine for patients with high-risk myelodysplastic syndromes?

DR YANG: Those are probably the most important findings reported in the past year on the treatment of MDS. The patients were randomly assigned to the hypomethylating agent azacitidine versus conventional care regimens, which were a choice of best supportive care, low-dose cytarabine or intensive chemotherapy. The profound survival advantage observed with azacitidine among these patients was surprising. The two-year survival rate doubled to more than 50 percent, and the median survival increased from 15 months to approximately 24 months (Fenaux 2009; [3.1]).

The old thinking in hematologic cancer was that we needed to achieve a complete response to obtain a survival benefit. However, these epigenetic therapies work differently than cytotoxic chemotherapy. At ASCO 2008 Alan List presented data demonstrating that patients who didn't achieve a complete response with azacitidine but did experience a partial response or hematologic improvement demonstrated a survival benefit (List 2008).

3.1

Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk Myelodysplastic Syndromes (MDS): Efficacy Data

	Azacitidine (n = 179)	CCR (n = 179)
Median overall survival	24.5 months	15 months
	HR = 0.58, $p = 0.0001$	
Median time to AML	17.8 months	11.5 months
	HR = 0.50, $p < 0.0001$	

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.

Tracks 6-8

DR LOVE: What is your initial approach for a patient with newly diagnosed MDS?

DR YANG: The majority of my practice is second opinions, and I believe that the most valuable action I can take for these patients is to take their slides to our hematopathologists for review. Pathologists in community hospitals are used to reviewing surgical biopsies, but bone marrow biopsies can be rare. The morphology in MDS is tricky and can be misdiagnosed.

Once the diagnosis of MDS is confirmed, I consider how I can cure the disease. In 2009, allogeneic transplant is probably the only way we can cure MDS. Unfortunately, most of the patients are older, and only approximately 10 percent are candidates for an allogeneic bone marrow transplant.

For patients younger than age 60 who are transplant eligible, one should consider consulting a transplant physician. The dilemma then is that the data are unclear as to whether we should use a hypomethylating agent before the transplant or simply send the patient directly to transplant.

It's also critical to stage the patient's disease, and I believe that the International Prognostic Scoring System (IPSS) is underused. Patients with low-risk disease will live for a long time, probably more than six years or even more than 10 years if they're younger than age 60. However, someone with high-risk disease has an expected survival of only three or four months.

Once we know the IPSS score, we can risk stratify the case and make treatment decisions. I also consider how the patient presents. Many patients simply go in for their annual physical and are found to be anemic. These patients fare much better than those who present with symptoms, regardless of their IPSS score, so I'm more conservative with patients who aren't experiencing symptoms.

DR LOVE: Would you review the IPSS system?

DR YANG: The IPSS uses three criteria: cytogenetic abnormalities, proportion of bone marrow myeloblasts and number of cytopenias. Points are assigned based on these variables and are added to create four risk groups: low, intermediate 1, intermediate 2 and high risk. If patients have more than 10 percent blasts in their bone marrow by morphology, they are automatically classified as having higher-risk MDS. Patients with chromosome 7 abnormalities, loss of chromosome 7 or complex cytogenetics typically also have high-risk MDS.

Another cytogenetic abnormality to watch for is the 5q-minus syndrome because these cases are highly responsive to lenalidomide, especially in patients at lower risk. Alan List made the clinical observation that lenalidomide works for patients with MDS associated with a chromosome 5q deletion (List 2006; [3.2]). It has high clinical activity for this type of MDS, almost comparable to imatinib in chronic myelogenous leukemia (CML).

Raza presented data on the activity of lenalidomide in patients with non-5q-minus MDS, and it seems to be active — although not as active — in those patients also. She reported a response rate of approximately 26 percent (Raza 2008; [3.2]). That number may be high because those patients were also receiving growth factors, but clearly activity occurs in patients without the 5q-minus karyotype.

Tracks 3-4, 9

DR LOVE: What is your treatment algorithm for MDS?

DR YANG: Because a survival benefit is clearly evident with the hypomethylating agents in higher-risk disease, I treat intermediate 2 or high-risk disease with one of these drugs first. For patients who are not experiencing symptoms and who present with low-risk disease, I am comfortable treating the anemia with growth factor support and monitoring them.

DR LOVE: How do you approach higher-risk disease that doesn't respond to one of the hypomethylating agents?

DR YANG: Azacitidine and decitabine are different chemically, and I've noticed, anecdotally, that patients whose disease doesn't respond or becomes refractory to one will respond to the other. The response is usually shorter and less dramatic, but clearly a response is evident. So I will either enroll such patients on a clinical trial or switch them to the other hypomethylating agent or lenalidomide. Most of my patients will receive all three of the FDA-approved drugs for MDS — azacitidine, decitabine and lenalidomide — at some point. The order is based on clinical or social needs at the time. ■

3.2

Erythroid Response to Lenalidomide in Myelodysplastic Syndromes (MDS) with Chromosome 5q Deletion and Karyotypes Other than Deletion 5q

	MDS with 5q deletion[1] (n = 148)	MDS with karyotypes other than deletion 5q[2] (n = 214)
Erythroid response		
Transfusion independence	67%	26%
≥50% decrease in number of transfusions	9%	17%
Total transfusion response	76%	43%
Median time to transfusion independence (range)	4.6 weeks (1-49)	4.8 weeks (1-39)
Hemoglobin		
Baseline*, median (range)	7.8 g/dL (5.3-10.4)	8.0 g/dL (6.1-10.6)
Response†, median (range)	13.4 g/dL (9.2-18.6)	11.6 g/dL (7.3-18.0)
Increase, median (range)	5.4 g/dL (1.1-11.4)	3.2 g/dL (1.0-9.8)

* Baseline hemoglobin concentration was the minimum value during the baseline period.

† Response hemoglobin concentration was the maximum value during the transfusion-independent response period.

SOURCES: [1] List AF et al. *N Engl J Med* 2006;355(14):1456-65; [2] Raza A et al. *Blood* 2008;111(1):86-93.

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Fenaux P et al. **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.

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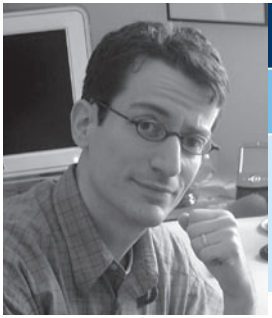
List AF et al. **Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion.** *N Engl J Med* 2006;355(14):1456-65.

Raza A et al. **Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q**. *Blood* 2008;111(1):86-93.



INTERVIEW

Michael J Mauro, MD

Dr Mauro is Associate Professor for the Center for Hematologic Malignancies at the Knight Institute at Oregon Health and Science University in Portland, Oregon.

Tracks 1-9

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss the biology of CML and how imatinib and the second-generation tyrosine kinase inhibitors affect it?

DR MAURO: CML is a unique type of cancer. It's the first tumor type linked to a single genetic abnormality — BCR-ABL. This is a well-described disease with a well-understood target, and the BCR-ABL oncogene is a central driver of CML.

When imatinib was under development, it seemed that it would be a clean therapeutic intervention, but based on other cancer models it was considered

impossible to obtain such a robust clinical benefit by inhibiting a cytogenetic or oncogenic marker alone.

Not only is imatinib highly active because it's such a potent BCR-ABL inhibitor, but also, when resistance is exhibited, it generally focuses around BCR-ABL.

As mechanisms of imatinib resistance were being investigated, the underlying question was whether they would be BCR-ABL independent or dependent. The fact that they're generally BCR-ABL dependent, with half the patients having mutations and others deriving clear clinical benefit from more powerful BCR-ABL inhibitors, means that not only in native disease but also in resistant disease, BCR-ABL is the driver (Kujawski 2007; [4.1]).

4.1

Imatinib Resistance in Chronic Myeloid Leukemia (CML)

"[Imatinib] resistance can be classified as BCR-ABL-dependent (eg, mutation in the BCR-ABL gene) or BCR-ABL independent (alternative pathways of disease progression, eg, SRC-family tyrosine kinases).

The investigation of therapeutic options post-imatinib failure resulted in the development and regulatory approval of dasatinib, a BCR-ABL and SRC-family kinase inhibitor. Dasatinib is active across all phases of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia, and demonstrates activity in almost all imatinib-resistant mutations.

Other therapeutic options are also under investigation, with nilotinib being the most clinically advanced. Nilotinib is an analog of imatinib with similar multiple kinase targets, but without inhibition of SRC, and reduced in vitro activity against BCR-ABL P-loop mutations compared with dasatinib.

Similar to dasatinib, nilotinib has no activity against T315I mutations. The availability of dasatinib and development of other tyrosine kinase inhibitors provide positive prospects for patients with imatinib-resistant or -intolerant CML."

SOURCE: Kujawski L, Talpaz M. *Leuk Lymphoma* 2007;48(12):2310-22.

Track 4

DR LOVE: How do you monitor patients with CML who have been treated with tyrosine kinase inhibitors?

DR MAURO: The way to follow patients with CML is to be careful about identifying toxicities while also being prompt to identify early on when they may not be charting an optimal course of response. We've seen from several studies that early intervention probably makes a difference.

Patients should demonstrate some cytogenetic response by six months. That's our minimum criterion. In essence, even patients who are faring well but not well enough at six months are probably charting a wrong course.

They will probably continue to fall off the curve and further beneath the curve and will possibly define themselves as failing therapy later on.

Tracks 4, 6

DR LOVE: Can you review the side-effect and toxicity profile of imatinib?

DR MAURO: In the early months to years of imatinib treatment, it's common for patients to experience mild fluid retention that often doesn't require intervention. Patients may have musculoskeletal complaints — bone pain or joint pain. Muscle cramps are also common.

These side effects can remain evident after years of treatment, but patients are willing to work through them because they don't seriously impair quality of life. Some patients experience gastrointestinal toxicities. These are avoidable, and we advise patients to take their imatinib with meals. We're also always on the lookout for some of the common yet manageable hematologic and biochemical toxicities.

DR LOVE: What about nilotinib and dasatinib?

DR MAURO: Nilotinib is a derivative of imatinib but does not yield some of the common imatinib-related side effects, such as fluid retention and musculoskeletal complaints. Patients can exhibit a rash or minor nonblood-related side effects.

Nilotinib can affect blood sugar, pancreatic enzymes and some of the salts we measure in the blood, such as phosphorus levels. Pancreatic enzyme elevation is unique to nilotinib, but it isn't necessarily a "deal breaker." It is infrequent, occurs early in treatment and is often a transient event. Clinical pancreatitis is rare. This is usually biochemical pancreatitis. Patients experience no pain, and no changes are evident on imaging. The condition can be resolved with a brief break in therapy or a reduced dose.

The unique toxicity with dasatinib that requires attention is a variety of fluid retention syndromes. Imatinib can cause visible edema — you can't miss it when patients walk in the door. Dasatinib can cause pleural effusions or pericardial effusions. These are correctable with early identification — a chest x-ray for a patient with any kind of symptoms. Stopping the drug for a while is probably the most important counterbalancing maneuver, but you can also administer steroids and diuretics to resolve an effusion.

Another factor with this family of drugs is that they can affect the QT or EKG electrical repolarization time. We need to screen patients before therapy to find out whether they have problems. If so, we might want to reconsider or at least monitor them on treatment. This is not a bad idea for any patient, but it applies by guidelines with nilotinib. This is also not a deal breaker in my view. If we're careful to screen patients and we follow them closely, this toxicity is unlikely to develop. ■

SELECT PUBLICATION

Kujawski L, Talpaz M. **Strategies for overcoming imatinib resistance in chronic myeloid leukemia.** *Leuk Lymphoma* 2007;48(12):2310-22.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the ECOG-E4A03 trial, low-dose dexamethasone in combination with lenalidomide was associated with _____ compared to high-dose dexamethasone in combination with lenalidomide.**
   a. Significantly fewer major toxicities
   b. A lower overall response rate
   c. Improvement in overall survival
   d. All of the above

2. **A study by Palumbo and colleagues reported a substantial decrease in bortezomib-related neurotoxicity with the weekly regimen compared to the twice-weekly regimen in patients with multiple myeloma.**
   a. True
   b. False

3. **Which of the following is a fully humanized anti-CD20 monoclonal antibody?**
   a. Ofatumumab
   b. Rituximab
   c. Both a and b

4. **In a clinical trial evaluating ofatumumab for fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory CLL, the overall response rate for patients who had previously received rituximab was in the range of _____ percent.**
   a. 20 to 24
   b. 30 to 34
   c. 50 to 54

5. **Czuczman and colleagues reported data from an international Phase II trial, NHL-003, that showed a _____ percent overall response rate with lenalidomide monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma.**
   a. 10
   b. 30
   c. 50

6. **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 syndromes.**
   a. Three months
   b. Nine months
   c. 12 months

7. **Lenalidomide is effective in treating MDS with 5q-minus syndrome.**
   a. True
   b. False

8. **Which of the following drugs is FDA approved for the treatment of myelodysplastic syndromes?**
   a. Azacitidine
   b. Decitabine
   c. Lenalidomide
   d. All of the above

9. **Which of the following therapeutic options are available for the treatment of CML for which imatinib has failed?**
   a. Nilotinib
   b. Dasatinib
   c. Both a and b

10. **Which of the following side effects are associated with imatinib treatment?**
    a. Fluid retention
    b. Musculoskeletal complaints
    c. Gastrointestinal toxicities
    d. All of the above

11. **In a Phase III study, first-line rituximab/bendamustine was equivalent in efficacy to R-CHOP for patients with follicular, indolent or mantle-cell lymphoma but was associated with significantly less alopecia and fewer infectious complications.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 4, 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
Weekly versus twice-weekly bortezomib in a Phase III study of VMPT versus VMP in newly diagnosed multiple myeloma	4 3 2 1	4 3 2 1
Phase III trial of R-CHOP-14 versus R-CHOP-21 for DLBCL	4 3 2 1	4 3 2 1
Clinical research with bevacizumab in DLBCL	4 3 2 1	4 3 2 1
Eligibility criteria for stem cell transplantation in the setting of hematologic cancer	4 3 2 1	4 3 2 1
AZA-001: Azacitidine compared to conventional care regimens in the treatment of higher-risk MDS	4 3 2 1	4 3 2 1
Implications of incomplete molecular remission in patients with chronic myelogenous leukemia	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:

- Identify patients with hematologic cancer who may be eligible for full- or reduced-intensity stem cell transplant . . . . . 4 3 2 1 N/M N/A
- Counsel patients with hematologic cancer about the incidence and management of side effects and toxicities associated with various systemic therapies. . . . . 4 3 2 1 N/M N/A
- Tailor up-front/induction therapy based on individual and disease characteristics for patients with multiple myeloma . . . . . 4 3 2 1 N/M N/A
- Develop evidence-based treatment algorithms for frequently encountered adult acute and chronic leukemias. . . . . 4 3 2 1 N/M N/A
- Educate patients with indolent or aggressive B-cell lymphomas about the benefits and risks of induction, consolidation and/or maintenance treatment strategies . . . . . 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 B- and T-cell non-Hodgkin lymphomas . . . . . 4 3 2 1 N/M N/A
- Use cytogenetics to individualize the clinical management of multiple myeloma, myelodysplastic syndrome and acute or chronic leukemia. . . . . 4 3 2 1 N/M N/A
- Recall the efficacy and side effects of hypomethylating and immunomodulating agents in the treatment of higher-risk myelodysplastic syndrome . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate . . . . . 4 3 2 1 N/M N/A

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

.....

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

.....

Additional comments about this activity:

.....

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

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

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

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Sergio Giralt, MD	4 3 2 1	4 3 2 1
Julie M Vose, MD	4 3 2 1	4 3 2 1
Allen SR Yang, MD, PhD	4 3 2 1	4 3 2 1
Michael J Mauro, 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 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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Hematologic Oncology™ UPDATE

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Hematologic Oncology™
UPDATE

This program is supported by educational grants from Celgene Corporation, Cephalon Inc, Eisai Inc, Genentech BioOncology/Biogen Idec, Genzyme Corporation, GlaxoSmithKline and Millennium Pharmaceuticals Inc.

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Sponsored by Research To Practice.

Last review date: November 2009
Release date: November 2009
Expiration date: November 2010
Estimated time to complete: 3 hours