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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Hematologic Oncology Update
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OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of evidence-based and current therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Use case-based learning to formulate individualized strategies for the care of patients with hematologic cancer.
- Develop an evidence-based treatment approach for younger and older patients with mantle-cell lymphoma.
- Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment.
- Summarize the critical factors in selecting patients with chronic myelogenous leukemia for treatment with first- and second-generation tyrosine kinase inhibitors.
- Employ an understanding of recent findings with proteasome inhibitors and immunomodulatory agents in individualized induction and maintenance therapy for patients with multiple myeloma.
- Develop an understanding of the mechanisms of action and the emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform future patients about protocol and nonprotocol options.
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.

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INTERVIEW

Ruben A Mesa, MD

Dr Mesa is Professor of Medicine and Chair of the Division of Hematology and Medical Oncology at the Mayo Clinic in Scottsdale, Arizona.

Tracks 1-13

Select Excerpts from the Interview

Tracks 1-4, 7-8

DR LOVE: Would you provide a brief overview of myeloproliferative neoplasms (MPNs) in general and more specifically of the evolution of JAK2 inhibitors in myelofibrosis (MF)?

DR MESA: I view MPNs as a group of chronic leukemias that can progress to acute leukemia. In MPNs, particularly in MF, the bone marrow becomes "leaky." Cells that ordinarily reside in the bone marrow leak out into the blood circulation and become trapped in the spleen. A misperception in the past has been that the spleen is enlarged as a result of anemia.

To provide some perspective, for a long time the only options for MF were either off-label medicines indicated for other cancers or clinical trials with agents being developed for other indications, such as myelodysplastic syndromes (MDS) or acute myeloid leukemia. Historically, we've had to "beg, borrow and steal" to have medicines to evaluate in MPNs. In large part, those trials were unsuccessful.

The watershed moment for these diseases came in 2005 when we started to make some inroads into understanding the pathogenesis of the disorders with the discovery of the JAK2 V617F mutation, which provided a "druggable target." JAK2 is part of the JAK-STAT pathway, which can be thought of as a tyrosine kinase pathway that acts as a stimulus for cells to grow and divide, parallel to our understanding of BCR-ABL in patients with chronic myeloid leukemia.

At this point, we believe the JAK2 mutation to be a "middle step" in the story. It's probably not the change that initiates the disease. Our understanding of the pathogenesis remains incomplete.

ASCO 2011 was particularly exciting in that it was the first time randomized Phase III trials have ever been performed in MF on any level, let alone with the success that was reported. Two important studies were presented, the first of which — and one for which I was a co-principal investigator — was ruxolitinib versus placebo for patients with intermediate- and high-risk MF.

This study demonstrated that ruxolitinib was quite potent in decreasing the massive splenomegaly associated with MF — a 42% improvement in this primary endpoint was observed versus placebo. Ruxolitinib was also potent in improving the significant symptoms that patients may experience with

1.1

Phase III Trial Results with the JAK1/2 Inhibitor Ruxolitinib for Patients with Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	COMFORT-I[1]		COMFORT-II[2]	
Efficacy — Primary endpoint	Ruxolitinib (n = 155)	Placebo (n = 153)	Ruxolitinib (n = 146)	BAT (n = 73)
Patients with ≥35% decrease in spleen volume at 24 weeks[1] and 48 weeks[2]	41.9%	0.7%	28.5%	0%
	$p < 0.0001$		$p < 0.001$	
Quality of life — Exploratory endpoint				
Patients with ≥50% decrease in symptom score	45.9%	5.3%	—	
	$p < 0.0001$			

BAT = best available therapy

Symptom score = sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the left ribs and early satiety

[1] Verstovsek S et al. *Proc ASCO* 2011;**Abstract 6500**; [2] Harrison CN et al. *Proc ASCO* 2011;**Abstract LBA6501**.

the illness, such as fatigue, night sweats and weight loss (Verstovsek 2011; [1.1]). Patients also experienced improvement in cachexia and recovery from abnormal decreases in their cholesterol.

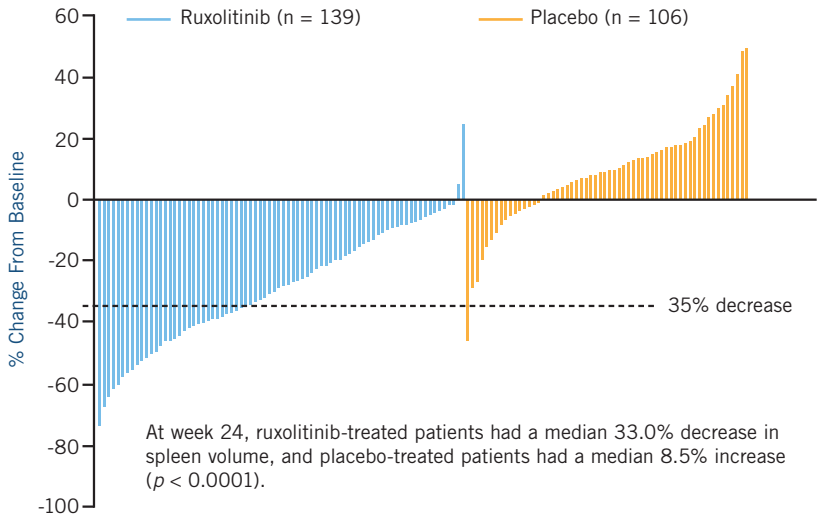
As we evaluate new agents, we ask ourselves: Does everyone benefit, or does a clear group benefit and another doesn't? I'd say with ruxolitinib and the other JAK2 inhibitors, we tend to see that the vast majority of patients experience a benefit. As we evaluate the waterfall plot, we see that the majority of patients have a decrease in spleen volume (Verstovsek 2011; [1.2]).

The other study presented was the European version of the trial — ruxolitinib versus physician's choice of alternative therapy in primary MF, postpolycythemia vera MF or postessential thrombocytopenia MF. Even against an active control arm of best available therapy, the results basically were interchangeable — dramatic improvements in the size of the spleen and a dramatic difference in terms of improvement in symptoms (Harrison 2011; [1.1]).

In terms of toxicities, both ruxolitinib and JAK2 inhibitors as a class across the spectrum of MPNs have variable degrees of myelosuppression. All the JAK2 inhibitors have a real dose-dependency issue, and we need to balance the need to administer enough JAK2 inhibitor to attain a benefit with that of avoiding dropping the red cell count or causing anemia or thrombocytopenia. For most of them, including ruxolitinib, the dose-limiting toxicity is thrombocytopenia. With the randomized study, we had already ascertained the optimal dosing, and 2 different dose levels were used depending on patients' platelet

1.2

COMFORT-I: Percent Change in Spleen Volume from Baseline in Response to Ruxolitinib versus Placebo in Patients with Myelofibrosis



With permission from Verstovsek S et al. *Proc ASCO* 2011;**Abstract 6500**.

counts. We found that anemia and thrombocytopenia were uncommon, with a prevalence of clearly less than 20% and in some cases less than 10% (Verstovsek 2011).

Track 9

DR LOVE: What role do immunomodulatory drugs (IMiDs) play in the treatment of MF?

DR MESA: All of the IMiDs — thalidomide, lenalidomide and now pomalidomide — have been active both in myeloma and MF. IMiDs have a variety of effects, but they certainly affect cytokines. Their benefit in MF has largely been improvement in cytopenias — anemia and thrombocytopenia. The current speculation is that inhibition of cytokines changes the bone marrow milieu and allows for more effective hematopoiesis to occur.

We've performed successful studies with lenalidomide in MF, and it is interesting that, like patients with MDS and deletion 5q, individuals with MF and deletion 5q can experience significant benefits with lenalidomide therapy (Tefferi 2007). Lenalidomide can also be helpful in other patients with MF, but the myelosuppressive effects of lenalidomide can sometimes be limiting.

Thus, we evaluated pomalidomide and found that low doses of pomalidomide are well tolerated and improve anemia and transfusion dependence in patients with MF (Tefferi 2009). The international Phase III RESUME trial is now evaluating pomalidomide versus placebo in more than 200 patients with MF and anemia.

DR LOVE: In which clinical situations have you used these agents for MF outside a protocol setting?

DR MESA: Thalidomide/prednisone is particularly effective in individuals with severe thrombocytopenia. I recently administered this combination to a patient with platelet transfusion dependence and anemia. I consider lenalidomide off study, particularly if a deletion 5q is in the karyotype or if the patient has refractory anemia. And unlike thalidomide, lenalidomide can potentially benefit patients with splenomegaly. ■

SELECT PUBLICATIONS

Harrison CN et al. **Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2011;**Abstract LBA6501**.

Tefferi A et al. **Pomalidomide is active in the treatment of anemia associated with myelofibrosis.** *J Clin Oncol* 2009;27(27):4563-9.

Tefferi A et al. **Lenalidomide therapy in del(5)(q31)-associated myelofibrosis: Cytogenetic and JAK2V617F molecular remissions.** *Leukemia* 2007;21(8):1827-8.

Verstovsek S et al. **Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF).** *Proc ASCO* 2011;**Abstract 6500**.

INTERVIEW

Robert Z Orlowski, MD, PhD

Dr Orlowski is Director of the Myeloma Section and Professor of Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-14

Track 1 Advances in proteasome inhibition for multiple myeloma (MM)

Track 2 Hypotheses for responsiveness to carfilzomib after bortezomib treatment

Track 3 Potential for combination proteasome inhibition in the treatment of hematologic cancer

Track 4 Carfilzomib, lenalidomide and dexamethasone (CRd) in newly diagnosed MM: Initial results of a Phase I/II study

Track 5 Benefits of subcutaneous bortezomib administration

Track 6 Bendamustine as a treatment option for relapsed MM

Track 7 Role of autologous stem cell transplant (ASCT) in the era of novel agents

Track 8 Perspective on the risk of second primary cancers with post-transplant maintenance lenalidomide in MM

Track 9 "Ascertainment bias" in detection of second primary cancers with post-transplant maintenance lenalidomide

Track 10 Consideration of resistance mechanisms to IMiDs in the debate regarding maintenance lenalidomide

Track 11 **Case discussion:** An 80-year-old woman with bone pain and pathologic fracture is diagnosed with del(13) and t(11;14) IgA lambda MM with 67% bone marrow plasma cells

Track 12 **Case discussion:** A 62-year-old man with high-risk del(13) and del(17p) IgA MM with 80% involvement of plasma cells in the bone marrow and acute renal failure receives induction CyBorD followed by ASCT and maintenance bortezomib/lenalidomide

Track 13 A proposed Intergroup study of lenalidomide, bortezomib and dexamethasone (RVD) induction followed by RVD maintenance versus RVD and elotuzumab induction followed by RVD and elotuzumab maintenance for high-risk MM

Track 14 Dose-reduced lenalidomide in patients with renal failure

Select Excerpts from the Interview

Tracks 1, 4-5

DR LOVE: Would you comment on the use of proteasome inhibition in multiple myeloma (MM)?

DR ORLOWSKI: The first proteasome inhibitor, bortezomib, was approved in 2003 for relapsed and refractory MM. Carfilzomib is a newer proteasome inhibitor, but it's different than bortezomib because, whereas bortezomib binds the proteasome and then lets go, carfilzomib is irreversible, and the degree or duration of inhibition is longer. Carfilzomib was evaluated in a Phase I trial and is undergoing Phase II testing, and it demonstrates activity in relapsed and refractory disease. It has a low risk of peripheral neuropathy (PN). Carfilzomib is administered intravenously, and studies suggest that bortezomib can be administered subcutaneously.

DR LOVE: What are your thoughts on the data presented at ASH 2010 on carfilzomib, lenalidomide and dexamethasone (CRd)?

DR ORLOWSKI: CRd is one of the best up-front therapies for newly diagnosed MM. The Phase I/II study by Dr Jakubowiak took lenalidomide/dexamethasone and added carfilzomib (Jakubowiak 2010; [2.1]). It was well tolerated and the response rates were excellent, but in Dr Richardson's data RVD has a 100% response rate (Richardson 2010). That's difficult to improve on.

DR LOVE: Another option to lower the risk of neuropathy is subcutaneous (SC) bortezomib. Any thoughts?

DR ORLOWSKI: A French trial was published of intravenous (IV) bortezomib with or without dexamethasone compared to SC bortezomib with or without

2.1

Carfilzomib/Lenalidomide/Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma

Clinical response	CRd (n = 27)
≥Partial response (PR)	96%
≥Very good PR	70%
Complete response (CR) or near CR	33%

Jakubowiak AJ et al. *Proc ASH* 2010;**Abstract 862**.

2.2

MMY-3021: A Phase III Trial of Subcutaneous (SC) versus Intravenous (IV) Administration of Bortezomib in Relapsed Multiple Myeloma

Response (n = 145, 73)	**Bortezomib SC**	**Bortezomib IV**
Overall response rate	42%	42%
Complete response	6%	8%
Nonhematologic adverse events (n = 147, 74)		
Any peripheral neuropathy (any grade)	38%	53%
Any peripheral neuropathy (Grade ≥3)	6%	16%

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

dexamethasone in relapsed MM (Moreau 2011; [2.2]). The response rates and the duration of response were similar, but SC dosing yielded a lower rate of PN. The lower rate of PN seen with SC bortezomib may be associated with the lower peak concentrations of the drug with SC dosing versus IV dosing.

Clearly, more studies with SC bortezomib are needed because so far we only have published results from one randomized trial in the relapsed setting. However, I don't know of a reason why the results would be any different in other disease settings, such as up-front therapy. Many of the trials of bortezomib that are now being planned are mandating SC dosing or at least allowing SC dosing, even those in the up-front setting.

I believe SC bortezomib is an important new standard, but until we see more data, I believe we should be a little cautious. In our practice, we are beginning to use SC bortezomib. From our experience it seems that patients are able to get in and out of their appointments more rapidly because they don't need an intravenous line put in, leading to less chair time.

Track 7

DR LOVE: What is the current role of autologous stem cell transplant (ASCT) in the era of novel agents in MM?

DR ORLOWSKI: This is a hot topic, and the IFM is leading a trial in which patients are receiving induction bortezomib/lenalidomide/dexamethasone followed by a randomization to transplant as up-front therapy or an option at relapse. It's a great study that we hope will answer the question, is up-front transplant still part of standard therapy?

In addition, at ASH 2010 data were presented from the ECOG study that compared lenalidomide with low-dose dexamethasone to lenalidomide with high-dose dexamethasone. Patients who underwent transplant as part of their initial therapy fared better (Siegel 2010).

Tracks 8-9

DR LOVE: What are your thoughts on the issue of post-transplant maintenance with lenalidomide?

DR ORLOWSKI: Two randomized studies — a trial from France and a trial from the CALGB — show a progression-free survival benefit of about 18 months with lenalidomide maintenance after transplant (2.3). However, both studies also show a small increase in second primary cancers in patients who received lenalidomide maintenance.

In the Spanish study of high-risk asymptomatic MM, in the patients who received lenalidomide/dexamethasone they found 2 secondary cancers (Mateos 2011). One was prostate cancer, and that patient in retrospect had an elevated PSA when the study started. The other was a JAK2-positive myeloproliferative

2.3

Post-Transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	Placebo (n = 307)	Lenalidomide (n = 231)	Placebo (n = 229)
Median PFS[1] or TTP[2]	41 mo	24 mo	48 mo	31 mo
	$p < 10^{-8}$		$p < 0.0001$	
	(n = 306)	(n = 302)	(n = 231)	(n = 229)
Second primary cancers				
Hematologic	11	3	8	0
Solid tumors	10	4	10	4

PFS = progression-free survival; TTP = time to progression

[1] Attal M et al. *Proc 13th International Myeloma Workshop* 2011; [2] McCarthy PL et al. *Proc 13th International Myeloma Workshop* 2011.

disorder, and before this patient received lenalidomide he had a JAK2 mutation. Some cases of MDS have been reported in addition to acute myeloid leukemia and solid tumors, so one has to be vigilant. One possible explanation is ascertainment bias, in that patients who receive placebo experience disease progression more rapidly and then come off trial. Follow-up on those patients is not as long, whereas because the other patients stay on study longer the follow-up is longer and it's easier to detect second cancers. I believe the issue of second primary cancers is less critical than has been touted, and until more data are available we haven't changed our recommendation. Ultimately we hope the additional planned studies will clarify whether a true risk exists. ■

SELECT PUBLICATIONS

Attal M et al. **Maintenance treatment with lenalidomide after transplantation for myeloma: Analysis of secondary malignancies within the IFM 2005-02 trial.** *Proc 13th International Myeloma Workshop* 2011.

Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of Phase I/II MMRC trial.** *Proc ASH* 2010;**Abstract 862**.

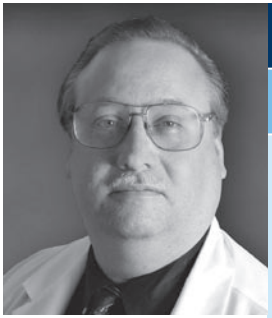
Mateos MV et al. **Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: A Phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (len-dex) as induction therapy followed by maintenance therapy with len alone vs no treatment.** *Proc ASH* 2011;**Abstract 991**.

McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB ECOG BMT-CTN 100104.** *Proc 13th International Myeloma Workshop* 2011.

Moreau P et al. **Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study.** *Lancet Oncol* 2011;12(5):431-40.

Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

Siegel DS et al. **Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial.** *Proc ASH* 2010;**Abstract 38**.



INTERVIEW

Myron S Czuczman, MD

Dr Czuczman is Chief of the Lymphoma/Myeloma Service and Head of the Lymphoma Translational Research Laboratory at Roswell Park Cancer Institute and is Professor of Medicine at the School of Medicine and Biomedical Sciences at the State University of New York at Buffalo in Buffalo, New York.

Tracks 1-13

Track 1 Clinical strategies with brentuximab vedotin in Hodgkin lymphoma

Track 2 **Case discussion:** A man in his late sixties who underwent triple coronary bypass surgery is diagnosed with ALK-negative anaplastic large cell lymphoma

Track 3 **Case discussion:** A 70-year-old woman with transformation of follicular lymphoma (FL) to diffuse large B-cell lymphoma experiences relapse 6 months after ASCT and responds to lenalidomide on a study

Track 4 Duration of lenalidomide for relapsed, aggressive lymphomas

Track 5 Role of lenalidomide in relapsed or refractory non-Hodgkin lymphoma

Track 6 Selection of initial therapy for Grade I/II (bendamustine/rituximab [BR]) and Grade III (R-CHOP) FL

Track 7 Bendamustine/rituximab (BR) in FL

Track 8 Perspective on the PRIMA trial results with maintenance rituximab in patients with high tumor burden FL responding to immunochemotherapy

Track 9 Approach to induction and maintenance therapy for patients with Grade I/II FL

Track 10 **Case discussion:** A fragile 85-year-old woman with multiple comorbidities presents with diffuse polyposis and gastrointestinal bleeding, is diagnosed with mantle-cell lymphoma (MCL) with extensive lymphadenopathy and achieves a complete response with BR

Track 11 Maintenance rituximab in elderly patients with MCL

Track 12 Front-line treatment approach for younger patients with MCL

Track 13 SWOG-S1106: A randomized Phase II study of R-hyper-CVAD or BR followed by ASCT for older patients with MCL

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the antibody-drug conjugate brentuximab vedotin in Hodgkin lymphoma?

DR CZUCZMAN: Brentuximab vedotin was recently approved by the FDA for patients with Hodgkin lymphoma who relapsed or experienced disease progres-

sion after ASCT. Brentuximab vedotin is a monoclonal antibody that binds CD30. When brentuximab vedotin binds a CD30-positive tumor cell it delivers the antimicrotubule agent monomethyl auristatin E inside the tumor cells.

Clinical trials are evaluating whether we can remove bleomycin from this setting. ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) is curative, but the lung toxicity is underestimated. The idea was to use AVD and add brentuximab vedotin, but it's similar to vinblastine so we need to determine whether this is optimal.

We want to avoid severe PN from combining 2 agents in the same family — the goal is less toxicity, not more. A theme in the future will be more frequent incorporation of these agents that are active in the refractory setting (3.1) in the up-front setting.

3.1

Response and Maximum Tumor Reduction with Brentuximab Vedotin (SGN-35) in Relapsed or Refractory Hodgkin Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL)*

	HL[1] (n = 102)	ALCL[2] (n = 58)
Overall response rate	75%	86%
Complete remission	34%	53%
Maximum tumor reduction (n = 96, 57)	94%	97%

* By independent review facility

[1] Chen R et al. *Proc ASCO* 2011;**Abstract 8031**.
[2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

Tracks 6-9

DR LOVE: What is your clinical decision-making algorithm for up-front treatment of follicular lymphoma (FL) in elderly patients?

DR CZUCZMAN: I generally use a watch-and-wait approach for older patients with comorbidities or those with limited disease. For an older patient in good shape, I try to minimize toxicity and go with bendamustine/rituximab (BR) unless other issues dictate more aggressive therapy.

I believe patients with Stage I/II disease should receive involved-field radiation therapy, but for patients with a fair amount of disease I'd probably administer BR. For patients with Grade I/II FL with low or low-intermediate FLIPI scores and no bad prognostic factors who are not eligible for a clinical trial, I also administer BR, and they exhibit favorable responses (Rummel 2010; [3.2]).

Many physicians are administering BR to patients with Grade I/II FL, but for patients with bulky disease, B symptoms or high-grade FLIPI scores I consider R-CHOP. For Grade III FL, anthracycline-based therapy should still be considered standard.

3.2

Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in Front-Line Indolent Lymphomas

	Overall response	Complete response	Progression-free survival	Median time to next treatment
BR (n = 260)	92.7%	39.6%	54.9 months	Not reached
R-CHOP (n = 253)	91.3%	30.0%	34.8 months	46.7 months
p-value	—	0.0262	0.00012	0.0281

Rummel MJ et al. *Proc ASCO* 2010. ASCO/ASH Joint Session.

DR LOVE: What are your thoughts on the use of rituximab maintenance in indolent lymphoma?

DR CZUCZMAN: It's controversial in that not all oncologists have embraced 2-year rituximab maintenance for all patients (Salles 2011).

For a patient at high risk, such as an elderly patient with fewer options, I administer rituximab maintenance if I'm concerned about early relapse, but it shouldn't be an automatic reaction for all patients.

DR LOVE: What about rituximab maintenance after BR?

DR CZUCZMAN: Most of the patients on the PRIMA study received R-CHOP, although some received R-CVP or R-FCM. We don't have data on BR with or without 2 years of rituximab maintenance.

A trial reportedly ongoing in Germany is administering BR and randomly assigning patients to 2 years of rituximab maintenance or nothing, and another trial in low-grade lymphoma will use "R squared" — rituximab and lenalidomide — or rituximab/chemotherapy. The patients who receive R squared will go on to R squared maintenance, and the patients who receive rituximab/chemotherapy will go on to rituximab maintenance.

The question is whether all patients need maintenance, however, and what the long-term effects are in terms of the tumor cell. My preference would be to use something different from what was initially used for induction, such as a novel noncross-resistant approach, to try to eradicate residual cells.

Track 13

DR LOVE: What are your thoughts on the SWOG trial of R-hyper-CVAD or BR prior to ASCT in mantle-cell lymphoma (MCL) (3.3)?

DR CZUCZMAN: It's an important study that goes against the premise of "more is better." It's astounding that so many patients are receiving R-hyper-CVAD — we're pushing the envelope with significant toxicity. Before bendamustine, some patients received fludarabine/rituximab and obtained complete responses too.

3.3

SWOG-S1106: A Randomized, Phase II Trial of R-Hyper-CVAD versus Bendamustine/Rituximab (BR) in Previously Untreated Mantle-Cell Lymphoma

Target Accrual: 180 (Open)

Eligibility

- Previously untreated Stage III, Stage IV or bulky Stage II mantle-cell lymphoma
- Age ≤65
- No central nervous system involvement
- Eligible for autologous stem cell transplant (ASCT)

Primary endpoint: 2-year progression-free survival
Secondary endpoints: Overall survival, objective response rate, safety

www.clinicaltrials.gov. Accessed December 5, 2011.

Do we have to use intensive therapy? Can we administer less toxic therapy up front? I'm anxious to see if we can obtain equivocal or better results or if we need to witness a lot of toxicity to achieve our goals. ■

SELECT PUBLICATIONS

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

Chen R et al. **Results of a pivotal Phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASCO* 2011;**Abstract 8031**.

Martinelli G et al. **Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98.** *J Clin Oncol* 2010;28(29):4480-4.

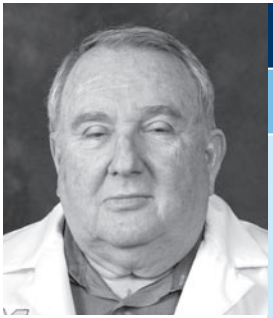
Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASCO* 2010. ASCO/ASH Joint Session.

Salles G et al. **Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial.** *Lancet* 2011;377(9759):42-51.

Shustov AR et al. **Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2010;**Abstract 961**.

Van Oers MH et al. **Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC 20981 phase III randomized intergroup study.** *J Clin Oncol* 2010;28(17):2853-8.

Younes A et al. **Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas.** *N Engl J Med* 2010;363(10):1812-21.



INTERVIEW

Moshe Talpaz, MD

Dr Talpaz is Alexander J Trotman Professor of Leukemia Research, Associate Director of Translational Research at the UM Comprehensive Cancer Center as well as Associate Chief of Hematology/Oncology and Director of Hematologic Malignancies at the University of Michigan Medical Center in Ann Arbor, Michigan.

Tracks 1-14

Track 1 Choice of initial tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia (CML)

Track 2 Selection of second-generation TKIs nilotinib or dasatinib for initial treatment of CML

Track 3 Potential influence of once-daily (dasatinib) versus twice-daily (nilotinib) dosing on patient adherence

Track 4 Complexities in comparing toxicities among imatinib, nilotinib and dasatinib

Track 5 Pathophysiology and treatment of dasatinib-associated pleural effusion

Track 6 Monitoring patients with CML who are receiving TKI therapy

Track 7 Defining the major goal of TKI treatment in CML: Complete cytogenetic remission with major molecular response

Track 8 Influence of side effects and patient age on adherence to TKI therapy in CML

Track 9 Relationship between compliance and inadequate response to TKI therapy in younger patients with CML

Track 10 Historical perspective on the treatments for MF

Track 11 JAK STAT signaling and the modes of action of JAK2 inhibitors

Track 12 JAK2 inhibitor-associated anticytokine and antiproliferative responses

Track 13 Durability and rates of response to ruxolitinib in patients with MF

Track 14 Side effects and quality of life with long-term ruxolitinib treatment for patients with MF

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is your approach to selection of first-line therapy for a patient with chronic myeloid leukemia (CML)?

DR TALPAZ: We start every patient with CML on a second-generation tyrosine kinase inhibitor (TKI), specifically nilotinib or dasatinib. As long as the cost differential between imatinib and these new agents is not large — and it isn't at this point — I see no reason to start a patient today on imatinib. That may change eventually when imatinib becomes generic, so we can reevaluate this discussion then based on financial grounds.

The outcome milestones that have been defined are driven primarily by results with imatinib, and they may have to be modified because the new agents are more efficient and attain results more quickly. Nevertheless, our expectations are that patients will at least have complete hematologic remission by 3 months, with normal counts and some minor cytogenetic response. This is what we call the European Leukemia Network criteria, and it is a good set of criteria likely to be adopted by the NCCN also.

DR LOVE: How might you choose — or how should an oncologist in practice choose — between nilotinib and dasatinib?

DR TALPAZ: These agents were studied in large Phase III studies, and they were not identical studies. To compare the results and say one agent is better than the other is unfair.

The results of the ENESTnd trial are somewhat superior, primarily in one aspect — rate of progression to accelerated or blast phase at 1 and 2 years on nilotinib compared to imatinib. The rate of progression was about 6% on imatinib. If we include clonal evolution, the rate of progression on 300 mg twice daily of nilotinib was only 0.7% (Kantarjian 2011a). In the DASISION study, by 2 years one started to see a bifurcation, and the rate of progression on imatinib was higher than on dasatinib (Kantarjian 2011b).

The rate of complete cytogenetic remission is similar between the studies. The rate of molecular responses is not dramatically different. Overall, it may well be that choice of agent should be based on toxicity rather than activity, and it will depend to a large degree on the patients.

Given a patient with lung disease, I would choose nilotinib. For a patient with pancreatic or liver disease, I would choose dasatinib. For a patient with significant fluid retention, I would opt for nilotinib. Given a patient with a history of migraines, I would not choose dasatinib because it can activate migraines. Basically, I would make the decision based not on activity of the agents but on how the patient will live with the drug.

Tracks 13-14

DR LOVE: What are your thoughts on the durability and rates of response with the novel JAK1/2 selective inhibitor ruxolitinib in MF?

DR TALPAZ: I worked not only with the COMFORT study but also with other JAK inhibitors. Most patients will respond to these agents. As far as symptoms, within a week patients feel better, and that's dramatic. The night sweats go away quickly, appetite improves and patients start to put on muscle. The reduction in spleen size is relatively quick (1.2, page 5).

Perhaps the more important issue is durability of response. Initially we thought these agents would only produce a trivial effect with rapid resistance. But I now have patients who are going for 4 years or more who are completely asymptomatic.

DR LOVE: What side effects have been reported with ruxolitinib?

DR TALPAZ: We deal with myelosuppression, which requires dose reduction/dose interruption. That's not a big factor in quality of life. Quality-of-life issues are diarrhea, fatigue, lack of energy, infections and so forth (Harrison 2011; [4.1]). Those are uncommon.

The quality of life, overall, is equal to or better than what we have seen with imatinib in CML. Granted, we may see other unique, rare toxicities with time, but the initial impression is that this is not chemotherapy. This is targeted therapy. ■

4.1

COMFORT-II Study: Common Nonhematologic Side Effects of the JAK1/2 Inhibitor Ruxolitinib in Patients with Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	Ruxolitinib (n = 146)		Best available therapy (n = 73)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	23%	1%	11%	0%
Peripheral edema	22%	0%	26%	0%
Asthenia	16%	1%	10%	1%
Dyspnea	16%	1%	18%	4%
Pyrexia	14%	2%	10%	0%
Nausea	13%	1%	7%	0%
Arthralgia	12%	1%	7%	0%
Fatigue	12%	1%	8%	0%

Harrison CN et al. *Proc ASCO* 2011;**Abstract LBA6501**.

SELECT PUBLICATIONS

Harrison CN et al. **Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2011;**Abstract LBA6501**.

Kantarjian HM et al. **Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.** *Lancet Oncol* 2011a;12(9):841-51.

Kantarjian H et al. **Dasatinib or imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Two-year follow-up from DASISION.** *Proc ASCO* 2011b;**Abstract 6510**.

Verstovsek S et al. **Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF).** *Proc ASCO* 2011;**Abstract 6500**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Ruxolitinib is a selective inhibitor of JAK1 and JAK2.**
   a. True
   b. False

2. **The Phase III COMFORT-I and COMFORT-II trials of ruxolitinib versus placebo and ruxolitinib versus best available therapy for MF did not demonstrate statistically significant and sustained reduction in spleen size in patients on the ruxolitinib study arms.**
   a. True
   b. False

3. **The Phase III RESUME trial is evaluating the efficacy and safety of _____ in patients with MF and red blood cell transfusion dependence.**
   a. Lenalidomide
   b. Thalidomide
   c. Pomalidomide

4. **Data from the MMY-3021 trial of SC versus IV bortezomib for patients with relapsed MM reported equivalent response rates and a(n) _____ incidence of PN with SC bortezomib.**
   a. Decreased
   b. Increased
   c. Equivalent

5. **The CALGB-100104 and IFM 2005-02 trials resulted in significant improvements in time to disease progression and progression-free survival with post-transplant lenalidomide maintenance among patients with newly diagnosed MM.**
   a. True
   b. False

6. **Brentuximab vedotin is an antibody-drug conjugate that targets _____ tumor cells.**
   a. CD20-positive
   b. CD30-positive
   c. CD5-positive

7. **Study data with brentuximab vedotin presented at ASH 2010 demonstrated an overall response rate of 75% or higher for patients with _____.**
   a. Hodgkin lymphoma
   b. Anaplastic large T-cell lymphoma
   c. Both a and b

8. **The SWOG-S1106 trial is evaluating induction therapy with R-hyper-CVAD followed by ASCT consolidation therapy versus _____ for patients with previously untreated MCL.**
   a. BR followed by ASCT
   b. R-CHOP
   c. Both a and b

9. **Which of the following is an approved treatment for patients with CML?**
   a. Dasatinib
   b. Imatinib
   c. Nilotinib
   d. All of the above

10. **Which of the following was (were) reported as among the most common nonhematologic adverse events associated with ruxolitinib therapy in the COMFORT-II trial?**
    a. Diarrhea
    b. Peripheral edema
    c. Fatigue
    d. All of the above
    e. None of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 4, 2011

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
Mechanism of action and activity of brentuximab vedotin in relapsed Hodgkin lymphoma	4 3 2 1	4 3 2 1
Efficacy, toxicity and duration of treatment with JAK2 inhibitors in MF	4 3 2 1	4 3 2 1
Role of IMiDs in the treatment of MF	4 3 2 1	4 3 2 1
CRd versus RVD in newly diagnosed MM	4 3 2 1	4 3 2 1
SWOG-S1106: A Phase II study of R-hyper-CVAD or BR followed by ASCT in younger patients with MCL	4 3 2 1	4 3 2 1
Clinical benefits and risk of second primary cancers with maintenance lenalidomide in MM	4 3 2 1	4 3 2 1
Maintenance rituximab in FL and MCL	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:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ 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:

- Use case-based learning to formulate individualized strategies for the care of patients with hematologic cancer..... 4 3 2 1 N/M N/A
- Develop an evidence-based treatment approach for younger and older patients with mantle-cell lymphoma..... 4 3 2 1 N/M N/A
- Counsel patients with follicular lymphoma about recent advances in induction and maintenance systemic treatment..... 4 3 2 1 N/M N/A
- Summarize the critical factors in selecting patients with chronic myelogenous leukemia for treatment with first- and second-generation tyrosine kinase inhibitors..... 4 3 2 1 N/M N/A
- Employ an understanding of recent findings with proteasome inhibitors and immunomodulatory agents in individualized induction and maintenance therapy for patients with multiple myeloma..... 4 3 2 1 N/M N/A

- Develop an understanding of the mechanisms of action and the emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform future patients about protocol and nonprotocol options. . . . . 4 3 2 1 N/M N/A
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.. . . . . 4 3 2 1 N/M N/A

Would you recommend this activity to a colleague?
☐ Yes ☐ No

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

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
Ruben A Mesa, MD	4 3 2 1	4 3 2 1
Robert Z Orlowski, MD, PhD	4 3 2 1	4 3 2 1
Myron S Czuczman, MD	4 3 2 1	4 3 2 1
Moshe Talpaz, 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

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