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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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EDITOR

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CONTENTS

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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

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with multiple myeloma.
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors and protein translation inhibitors as therapeutic options for patients with chronic myeloid leukemia.
- Develop an understanding of emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform patients regarding protocol and nonprotocol treatment options.
- Counsel patients with follicular and mantle-cell lymphoma about recent advances in induction and maintenance systemic treatment, and integrate these advances into current treatment algorithms as appropriate.
- Describe the biologic rationale for and emerging roles of novel and approved antibody-drug conjugates — alone and in combination with chemotherapy — in the treatment of Hodgkin lymphoma, acute lymphoblastic leukemia and other CD30- or CD22-positive hematologic disorders.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

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INTERVIEW

Michael E Williams, MD, ScM

Dr Williams is Byrd S Leavell Professor of Medicine and Chief of the Hematologic Malignancies Section at the Hematology/Oncology Division and Cancer Center at the University of Virginia School of Medicine in Charlottesville, Virginia.

Tracks 1-19

Track 1 ECOG-E4402: RESORT trial comparing rituximab maintenance to rituximab re-treatment upon disease progression for low tumor burden indolent non-Hodgkin lymphoma

Track 2 Activity and current indications for ofatumumab in relapsed or refractory chronic lymphocytic leukemia (CLL)

Track 3 Efficacy of lenalidomide alone and in combination with rituximab in indolent and aggressive lymphomas

Track 4 Novel agents under investigation in B-cell lymphomas: the PI3 kinase inhibitor GS-1101 (CAL-101) and the Bruton tyrosine kinase inhibitor (TKI) ibrutinib (PCI-32765)

Track 5 Use of radioimmunotherapy (RIT) as up-front and consolidation therapy in follicular lymphoma (FL)

Track 6 Approved and investigational treatment options for patients with CLL

Track 7 Challenges associated with the use of FCR; activity and tolerability of bendamustine/rituximab (BR) in CLL

Track 8 Diffuse large B-cell lymphoma (DLBCL): Overview of distinct subtypes and differential outcomes

Track 9 Role of interim and post-treatment PET scanning for patients receiving treatment for DLBCL

Track 10 Indications for central nervous system prophylaxis and treatment for patients with DLBCL and cardiac dysfunction or HIV infection

Track 11 **Case discussion:** A 76-year-old man with elevated white blood cell count and splenomegaly without significant lymphadenopathy is initially diagnosed with CLL but flow cytometry confirms indolent mantle-cell lymphoma (MCL) with 11;14 translocation

Track 12 Perspective on the "watch-and-wait" strategy for patients with indolent MCL

Track 13 Intergroup study of BR versus BR with bortezomib with or without lenalidomide maintenance therapy for older patients (≥60 years) with newly diagnosed MCL

Track 14 Intergroup study of R-hyper-CVAD versus BR followed by autologous stem cell transplant (ASCT) for younger patients (≤65 years) with newly diagnosed MCL

Track 15 Current indications and potential roles for bortezomib in MCL

Track 16 Survival benefit with rituximab versus interferon as maintenance therapy after R-CHOP in elderly patients with MCL

Track 17 Front-line treatment approach for younger patients with MCL

Track 18 Induction therapy options for nontransplant-eligible patients with MCL and the role of maintenance rituximab therapy

Track 19 **Case discussion:** A 55-year-old woman with nonblastoid Stage IVB MCL who experiences disease relapse 18 months after treatment with R-hyper-CVAD and ASCT attains a complete remission with ibrutinib on a clinical trial

Select Excerpts from the Interview

Track 1

DR LOVE: Would you provide an update of recent clinical trial results in indolent and follicular lymphoma?

DR WILLIAMS: The most important developments relate to the studies in low tumor burden follicular lymphoma (FL). This was the focus of the RESORT trial, which evaluated patients who could traditionally be offered "watch and wait" and deferred therapy. Four doses of rituximab were administered, and those patients who responded — with either partial or complete remission — were randomly assigned to indefinite maintenance every 3 months until disease progression or re-treatment with rituximab upon progression.

We found no benefit with maintenance compared to re-treating as necessary (Kahl 2011) and confirmed what other studies suggested — that patients may go 3 years or beyond with only 4 doses of rituximab and not experience recurrence. For patients with higher tumor burden FL who are symptomatic and need therapy, the PRIMA study indicated a benefit with rituximab maintenance after rituximab/chemotherapy (Salles 2011). These 2 are the highest-impact data sets that have emerged in this tumor type.

DR LOVE: Many investigators have told me that the findings of the control arm of the RESORT trial with 4 doses of rituximab were so impressive that they are now less likely to use watch and wait for patients with low tumor burden FL. Any thoughts?

DR WILLIAMS: I expect over time we will see that trend. In my practice, for asymptomatic patients with low tumor burden FL I typically discuss watch and wait and try to determine the pace of the disease. If patients are comfortable with that and prefer to be followed without treatment, that's fine. If they are more secure in proceeding with treatment, however, 4 doses of rituximab without maintenance is justified by the Phase III data, and the hope is that, particularly for older patients, chemotherapy may be delayed or not needed.

DR LOVE: What about the clinical practice issue of maintenance rituximab for patients with high tumor burden who receive rituximab/chemotherapy up front?

DR WILLIAMS: This approach has been widely adopted, and I believe maintenance for 2 years after induction is reasonable and an important option for discussion.

Track 5

DR LOVE: Continuing on in terms of indolent lymphoma — anything new regarding radioimmunotherapy (RIT)?

DR WILLIAMS: Yttrium-90 ibritumomab tiuxetan and ^{131}I-tositumomab are the 2 most active single treatments in relapsed FL. We use them in older patients, and you can complete treatment in 1 week. Response rates are high, and some patients experience durable responses. RIT has also been used as consolidation. Mitchell Smith recently published the results of an ECOG trial in mantle-cell lymphoma (MCL) with 4 doses of R-CHOP followed by RIT (Smith 2012), and it's safe and effective. How it compares to other approaches, such as rituximab maintenance, is unknown.

Based on the data from the FIT trial, it is also useful as consolidation for patients with FL who have achieved either a complete or a partial remission (Hagenbeek 2010). It's also being tested as whole body radiation therapy by using high doses of RIT for patients who are heading to autologous stem cell transplant (ASCT) (NCT00110071).

The Phase III SWOG-S0016 study evaluating R-CHOP versus CHOP followed by ^{131}I-tositumomab reported similar outcomes between the 2 arms (Press 2011), but

perhaps with additional maintenance one can build on the response and provide patients with better durability of remission.

Tracks 12-14

DR LOVE: Let's talk about MCL, beginning with your thoughts on the small proportion of patients who can be observed off treatment initially. What is your clinical experience?

DR WILLIAMS: A lot of patients come in having read about and having been told that they must proceed to therapy — that MCL is a bad disease. So it takes education to talk them down, and I see a considerable amount of second opinions and consults.

One man had received 3 opinions before he saw me. One physician had recommended R-CHOP, and 2 had recommended transplant — one immediate transplant after induction and the other planning transplant but potentially deferring it. However, the disease was clearly indolent. He'd been aware of some nodes that hadn't changed much for more than 2 years, had a low Ki-67 score and was asymptomatic. He was in his late sixties, healthy and active, so I recommended observation. After 2 years he developed disease progression and recently completed 1 course of bendamustine/rituximab (BR). He's in complete remission now, 4 years since we met.

DR LOVE: What are some of the key ongoing clinical trials in MCL?

DR WILLIAMS: We don't have a standard therapy for MCL, but we have a variety of active approaches. Some controversy surrounds how best to induce patients and how to sequence therapies, so clinical trials are a high priority.

Two trials in the United States are important now (1.1). One is the ECOG-E1411 study, predominantly for older patients and those who are not transplant candidates, and what we're testing in this group is a BR backbone. The patients receive either BR or bendamustine/bortezomib/rituximab induction therapy, and then they are randomly assigned to 1 of 2 different maintenance options, either rituximab alone or the R-squared regimen — lenalidomide and rituximab (1.1). For transplant-eligible patients, the SWOG-S1106 trial will compare BR to R-hyper-CVAD with methotrexate and cytarabine (Ara-C). Patients with responses will then undergo ASCT.

1.1

Phase II Intergroup Studies for Patients with Previously Untreated Mantle-Cell Lymphoma

Trial identifier	N	Age of patients	Treatment arms
SWOG-S1106 NCT01412879	180	≤65 years	• R-hyper-CVAD/MTX/Ara-C → ASCT • BR → ASCT
ECOG-E1411 NCT01415752	332	≥60 years	• BR → R • BVR → R • BR → LR • BVR → LR

MTX = methotrexate; ASCT = autologous stem cell transplant; B = bendamustine; R = rituximab; V = bortezomib; L = lenalidomide

www.clinicaltrials.gov. Accessed November 15, 2012.

Track 16

DR LOVE: What do we know about rituximab maintenance in MCL, and how do you approach this issue in practice?

DR WILLIAMS: The European Mantle-Cell Network has been extremely effective in conducting Phase III trials. The nontransplant study in older patients was recently reported in *The New England Journal of Medicine* by Dr Kluin-Nelemans (1.2).

They evaluated R-CHOP versus rituximab/fludarabine/cyclophosphamide (R-FC) induction followed by either interferon or rituximab maintenance and found that R-FC was more toxic and less efficacious than R-CHOP. For patients receiving R-CHOP, the benefit was clear in terms of duration of response and survival with rituximab maintenance versus interferon until progression.

With that we've adapted rituximab maintenance after induction therapy in our nontransplant patients. I'm using it both for patients who receive R-CHOP and for patients who've received BR induction. ■

1.2 **Rituximab Maintenance versus Interferon Alpha for Elderly Patients with Mantle-Cell Lymphoma: Efficacy and Toxicity Among Patients Responding to R-CHOP Induction**

Response	Rituximab	Interferon	*p*-value
Median remission duration	Not reached	23 mo	<0.001
Four-year overall survival rate	87%	63%	0.005
Select Grade 3 and 4 toxicities			
Leukocytopenia	4%	18%	—
Lymphocytopenia	27%	46%	—

Kluin-Nelemans HC et al. *N Engl J Med* 2012;367(6):520-31.

SELECT PUBLICATIONS

Hagenbeek A et al. **90Y-ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, Phase III First-Line Indolent Trial (FIT) in 414 patients.** *Proc ASH* 2010;**Abstract 594**.

Kahl BS et al. **Results of Eastern Cooperative Oncology Group protocol E4402 (RESORT): A randomized Phase III study comparing two different rituximab dosing strategies for low tumor burden follicular lymphoma.** *Proc ASH* 2011;**Abstract LBA-6**.

Kluin-Nelemans HC et al. **Treatment of older patients with mantle-cell lymphoma.** *N Engl J Med* 2012;367(6):520-31.

Press O et al. **A Phase III randomized Intergroup trial (SWOG S0016) of CHOP chemotherapy plus rituximab vs CHOP chemotherapy plus iodine-131-tositumomab for the treatment of newly diagnosed follicular non-Hodgkin's lymphoma.** *Proc ASH* 2011;**Abstract 98**.

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.

Smith MR et al. **Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by yttrium-90-ibritumomab tiuxetan in untreated mantle-cell lymphoma: Eastern Cooperative Oncology Group study E1499.** *J Clin Oncol* 2012;30(25):3119-26.

INTERVIEW

P Leif Bergsagel, MD

Dr Bergsagel is Grohne Professor of Therapeutics in Cancer Research at Mayo Clinic Arizona in Scottsdale, Arizona.

Tracks 1-14

Track 1 Lack of peripheral neuropathy with the newly FDA-approved irreversible proteasome inhibitor carfilzomib in multiple myeloma (MM)

Track 2 Impact of cytogenetics on approach to induction and post-transplant consolidation and maintenance therapy

Track 3 Key high-risk cytogenetic abnormalities: t(4;14) and 17p deletion

Track 4 Influence of depth of response on post-transplant consolidation and maintenance therapy

Track 5 Incorporating carfilzomib into induction treatment for newly diagnosed MM

Track 6 Mechanism of action of proteasome inhibitors

Track 7 Potential future roles for the orally bioavailable proteasome inhibitor MLN9708 and the immunomodulatory drug pomalidomide under development in MM

Track 8 Cereblon: A direct protein target for immunomodulatory and antiproliferative actions of lenalidomide and pomalidomide

Track 9 Perspectives on the MRC Myeloma IX study of zoledronic acid in patients with MM with or without bone disease and duration of bisphosphonate therapy

Track 10 Responses and tolerability with the novel monoclonal antibodies elotuzumab and daratumumab in MM

Track 11 **Case discussion:** A 55-year-old woman with symptomatic, hyperdiploid ISS Stage I MM attains a partial response to Rd, and the referring physician wishes to switch to a bortezomib-containing regimen prior to ASCT

Track 12 Up-front treatment for transplant-ineligible patients with MM and those with adverse cytogenetics

Track 13 **Case discussion:** A 68-year-old man who received treatment for MM in 2003 presents with lytic bone lesions in the humerus and femur and switches from RVD therapy to RD after 2 cycles due to neuropathy

Track 14 **Case discussion:** A 62-year-old man with symptomatic ISS Stage III MM with a 17p deletion

Select Excerpts from the Interview

Tracks 1, 5

DR LOVE: Would you comment on the newly FDA-approved agent carfilzomib in multiple myeloma?

DR BERGSAGEL: Carfilzomib is a novel irreversible proteasome inhibitor that seems to have activity similar to bortezomib, but it's hard to know if it's better. It's active in some patients with relapsed or bortezomib-refractory disease, although the response rate is lower in that setting (Vij 2012a, 2012b). The side-effect profile of carfilzomib is also different. Neuropathy, which is a big concern for a lot of patients receiving bortezomib, is not significant with this agent.

Although preliminary, data with the combination of lenalidomide, dexamethasone and carfilzomib are exciting, showing exceptionally high and deep response rates in the up-front setting (Jakubowiak 2012; [2.1, 2.2]). However, more data are needed to make these results conclusive. We participated in the Phase I/II trial of carfilzomib, and since its approval, I've administered it.

DR LOVE: In your practice, can you discern less neuropathy than with bortezomib, or is this discernible more from the trial data?

DR BERGSAGEL: With the use of weekly or subcutaneous bortezomib neuropathy seems to be less of a problem than it used to be. Patients from other practices who are receiving twice-a-week intravenous bortezomib are being referred to me and I see that they're having problems with neuropathy. However, the issue of neuropathy in myeloma is diminishing. I haven't observed problems with neuropathy in patients

2.1

Phase I/II Trial of Carfilzomib in Combination with Lenalidomide and Low-Dose Dexamethasone (CRd) as Front-Line Therapy for Transplant-Eligible and Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (MM)

Parameter	≥PR	≥VGPR	≥nCR	sCR
All patients (n = 53)	98%	81%	62%	42%
Treatment duration				
≥4 cycles (n = 49)	100%	88%	67%	45%
≥8 cycles (n = 36)	100%	92%	78%	61%
≥12 cycles (n = 29)	100%	86%	72%	62%
Cytogenetics*				
Normal/favorable (n = 34)	100%	76%	59%	38%
Unfavorable (n = 17)	94%	76%	65%	53%

* Unfavorable: Del13 by metaphase, hypodiploidy, t(4;14), t(14;16) or del17p; normal/favorable: All others

PR = partial response; VGPR = very good PR; nCR = near complete response; sCR = stringent complete response

Conclusions: The CRd regimen was well tolerated and highly active as front-line therapy for patients with newly diagnosed MM. These results will require validation in the randomized controlled setting to definitively demonstrate the benefit of adding carfilzomib to Rd. A Phase III trial of CRd compared to Rd for the treatment of relapsed MM (ASPIRE) is ongoing.

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

2.2

Select Adverse Events During CRd Induction in Patients with Multiple Myeloma

Adverse events (n = 53)	Any grade	Grade 3 or 4
Nonhematologic		
Hyperglycemia	72%	23%
Hypophosphatemia	45%	25%
Fatigue	38%	2%
Muscle cramping	32%	0%
Peripheral neuropathy	23%	0%
Hematologic		
Thrombocytopenia	68%	17%
Anemia	60%	21%
Neutropenia	30%	17%

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

receiving carfilzomib in my practice. So it's not just the trial data. It's also reflected in my own experience.

DR LOVE: Based on what is known about carfilzomib from the clinical trials, would you consider recommending it off protocol in the up-front setting?

DR BERGSAGEL: I would eagerly participate in a trial of carfilzomib but would not use it off protocol in the up-front setting yet. I would like to see more data about its safety profile in more patients. If I had a patient who already had neuropathy and I wanted to use a proteasome inhibitor, only then would I consider administering carfilzomib up front because I would have a clear reason in that situation.

Track 10

DR LOVE: A lot of exciting developments have occurred in a number of cancers with monoclonal antibodies but not much until recently in myeloma. What is known about elotuzumab and daratumumab?

DR BERGSAGEL: Elotuzumab is an antibody to cell surface glycoprotein CS1. It didn't show significant single-agent activity in a Phase I clinical trial (Zonder 2012), but it appears promising when examined in combination with lenalidomide and dexamethasone in the relapsed setting (Lonial 2012). I believe elotuzumab is one of the most exciting antibodies under investigation in multiple myeloma.

Daratumumab is an anti-CD38 monoclonal antibody that seems to have single-agent activity. The results were recently presented at ASCO, and the dose-limiting toxicity is yet to be reached (Plesner 2012). At the higher doses of the antibody, the investigators observed partial and minor responses in the relapsed or refractory setting. So I would say that daratumumab is even more exciting because it seems to have single-agent activity. ■

SELECT PUBLICATIONS

Jagannath S et al. **An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma.** *Clin Lymphoma Myeloma Leuk* 2012;12(5):310-8.

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801-9.

Lonial S et al. **Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma.** *J Clin Oncol* 2012;30(16):1953-9.

Plesner T et al. **Daratumumab, a CD38 mab, for the treatment of relapsed/refractory multiple myeloma patients: Preliminary efficacy data from a multicenter phase I/II study.** *Proc ASCO* 2012;**Abstract 8019**.

Richardson PG et al. **Management of treatment-emergent peripheral neuropathy in multiple myeloma.** *Leukemia* 2012;26(4):595-608.

Siegel DS et al. **A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma.** *Blood* 2012;120(4):2817-25.

Vij R et al. **An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma.** *Blood* 2012a;119(24):5661-70.

Vij R et al. **An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib.** *Br J Haematol* 2012b;158(6):739-48.

Zonder JA et al. **A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma.** *Blood* 2012;120(3):552-9.

INTERVIEW

Jorge E Cortes, MD

Dr Cortes is DB Lane Cancer Research Distinguished Professor for Leukemia Research and Deputy Chairman and Section Chief of AML and CML in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-21

Track 1 Efficacy, side effects and mechanism of action of the antibody-drug conjugate inotuzumab ozogamicin for relapsed or refractory acute lymphoblastic leukemia (ALL)

Track 2 Effect of the bispecific T-cell engaging (BiTE) antibody blinatumomab on complete remission rate in patients with relapsed or refractory B-precursor ALL

Track 3 Assessment of BCR-ABL1 transcript levels at 3 months as a predictor of favorable outcomes for patients with chronic myeloid leukemia (CML) treated with TKIs

Track 4 Monitoring responses in patients with CML receiving TKI therapy

Track 5 Selection of a second-generation TKI — nilotinib or dasatinib — for initial treatment of CML

Track 6 Mutational analysis in patients with CML

Track 7 PACE: Results from a Phase II trial of the newly FDA-approved agent ponatinib in patients with CML and Philadelphia chromosome-positive (Ph+) ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation

Track 8 Efficacy of the newly FDA-approved oral second-generation TKI bosutinib for patients with chronic-, accelerated- or blast-phase Ph+ CML with resistance or intolerance to prior therapy

Track 9 Effectiveness of the newly FDA-approved protein translation inhibitor omacetaxine for patients with chronic- and accelerated-phase CML whose disease has progressed on 2 or more TKIs

Track 10 Accurate diagnosis and staging of myelofibrosis (MF)

Track 11 Use of prognostic scoring systems — International Prognostic Scoring System (IPSS) and Dynamic IPSS (DIPSS) — to predict outcomes for patients with MF

Track 12 Long-term outcomes for patients with MF receiving the JAK1/JAK2 inhibitor ruxolitinib — survival advantage in comparison to matched historical controls

Track 13 Overview of JAK inhibitor therapy in MF: Patient eligibility, activity in JAK mutation-positive and mutation-negative disease and potential predictors of response and resistance

Track 14 Update on selective JAK inhibitors currently under investigation in MF

Track 15 Importance of symptom and side-effect monitoring in patients receiving treatment for MF

Track 16 Monitoring responses and indicators for switching therapy in patients with CML treated with imatinib

Track 17 Activity of ponatinib in patients with CML experiencing disease progression after treatment with imatinib, dasatinib and nilotinib

Track 18 Duration of treatment with JAK2 inhibitors in MF

Track 19 Titration of ruxolitinib dose based on platelet count

Track 20 Therapeutic options for younger patients with ALL who experience rapid disease relapse

Track 21 Activity of FLT3 inhibitors alone and in combination with chemotherapy for relapsed or refractory acute myeloid leukemia

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you talk about the clinical activity of the novel agents inotuzumab ozogamicin and blinatumomab in acute lymphoblastic leukemia (ALL)?

DR CORTES: Inotuzumab ozogamicin is an investigational immunoconjugate that targets CD22, an antigen expressed in more than 90% of patients with ALL. The anti-CD22 antibody is attached to the toxin calicheamicin. A high durable response rate was observed in patients with ALL for whom other therapies had failed (Jabbour 2012; [3.1]). Some of these patients can be taken to transplant and thus have the potential of a cure. Liver toxicity is observed in a small proportion of patients, but it is rarely serious.

Blinatumomab is a bispecific T-cell engaging (BiTE) antibody that is designed to direct cytotoxic T cells to CD19-expressing ALL cells. A recent ASCO presentation reported responses in more than 50% of patients, with some patients experiencing complete remissions (Topp 2012; [3.2]). This agent also has been shown to have activity in patients with minimal residual disease.

3.1

Inotuzumab Ozogamicin, Administered Weekly, for Relapsed/Refractory Acute Lymphoblastic Leukemia

Response	N = 27
Overall response rate	52%
Complete response (CR)	11%
CRp (CR except platelets)	30%
Marrow CR	11%
Resistant	41%

Jabbour E et al. *Proc ASCO* 2012;**Abstract 6501**.

3.2

Effect of the Anti-CD19 BiTE Blinatumomab on Complete Remission Rate Among Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia

Response	All cohorts (N = 36)	Cohorts 2a + 3* (n = 23)
CR/CRh	72%	74%
Complete remission (CR)	44%	48%
CRh (CR with partial hematologic recovery)	28%	26%

* Final dose 5 μg/m^2 per day during week 1 and 15 μg/m^2 per day for the remaining treatment

Topp MS et al. *Proc ASCO* 2012;**Abstract 6500**.

Tracks 3-4

DR LOVE: Would you discuss your recent *JCO* editorial (Cortes 2012a) entitled, "Not only response but early response to tyrosine kinase inhibitors in chronic myeloid leukemia"?

DR CORTES: Because therapy for chronic myeloid leukemia (CML) has improved, we now want responses that are durable and patient survival that extends well beyond 5 years. Patients who have the best responses to tyrosine kinase inhibitor (TKI) therapy at 3 months, by cytogenetics or by molecular testing, are the ones who are more likely to have good outcomes in the long term (Marin 2012). So the major point I wanted to emphasize in the editorial is that an early response to TKI therapy is a good predictor of a durable response and longer survival.

DR LOVE: What algorithm do you follow for monitoring response in CML, and how does it affect your decision regarding which TKIs you use?

DR CORTES: At baseline, a bone marrow aspiration should be performed to make sure that the patient's disease is appropriately staged. It is important to do a cytogenetic analysis at least by FISH and PCR at 3, 6 and 12 months from the start of treatment to determine response. Once a complete cytogenetic response and a major molecular response are achieved, monitoring can be continued every 6 months.

I administer second-generation TKIs for all my patients as initial therapy because they offer a better outcome than imatinib. However, imatinib is recommended in many settings, and the fact that a generic version will be available soon is beneficial. Early monitoring becomes critical because by identifying patients who are faring well at 3 months, you don't have to worry about the second-generation TKIs.

If a patient does not have a good molecular or cytogenetic response at 3 months, the patient is unlikely to fare well in the long term. The other question that arises is, what agent could be used to improve outcomes in this setting? If the patient is receiving imatinib, then dasatinib or nilotinib could be used as salvage therapy. If dasatinib or nilotinib are used for treatment, no other agent is significantly more effective. The newly FDA-approved drug ponatinib is active in the salvage setting when other therapies have failed and is now an option for these patients.

Tracks 7-9

DR LOVE: Would you discuss what is known about the efficacy and side effects of ponatinib and the other newly FDA-approved agents bosutinib and omacetaxine in CML?

DR CORTES: Ponatinib, bosutinib and omacetaxine are interesting agents because they offer us additional tools to manage CML.

Ponatinib is a third-generation TKI that is effective in patients with the T315I mutation. We reported the results of a Phase II study at ASCO 2012, which indicated that about 60% of patients whose disease is resistant to other TKIs respond to ponatinib (Cortes 2012b). A major cytogenetic response to ponatinib was observed in approximately 70% of patients with the T315I mutation. So it has potential in this setting. The dose-limiting toxicity for ponatinib is pancreatitis. At the 45-mg dose used in the Phase II study, less than 10% of patients develop pancreatitis. Ponatinib is a well-tolerated drug overall, with a toxicity profile similar to other drugs in this setting.

Bosutinib is a second-generation TKI. It does not inhibit the T315I mutation, but about 30% of patients whose disease failed to respond to prior TKI therapy respond to bosutinib (Khoury 2012; [3.3]). The toxicity profile is favorable. It causes transient diarrhea, which is manageable. Liver toxicity may occur, so liver enzymes need to be monitored.

3.3

Activity of Bosutinib in Chronic-Phase Chronic Myeloid Leukemia After Disease Progression on Imatinib and Dasatinib and/or Nilotinib Therapy

Endpoint	
Hematologic response (n = 116)*	
Complete response	73%
Cytogenetic response (n = 108)*	
Major response	32%
Complete response	24%
Molecular response (n = 105)*	
Major response	15%

* Total number of evaluable patients out of 118 patients enrolled in study
Responses were seen across BCR-ABL mutations, including those associated with dasatinib and nilotinib resistance, except T315I.

Khoury HJ et al. *Blood* 2012;119(15):3403–12.

Omacetaxine acts by inhibiting the synthesis of proteins and is effective in patients with the T315I mutation. It can be effective in about 25% of patients, even when other agents have failed (Cortes 2012c; [3.4]). So it'll be a useful drug for a subset of patients with CML who will need an agent other than a TKI to achieve a response. Omacetaxine is a little more myelosuppressive than the other drugs, but it does not have any significant side effects.

3.4

Phase II Study of Omacetaxine After Tyrosine Kinase Inhibitor Failure in Patients with Chronic-Phase Chronic Myeloid Leukemia with the T315I Mutation

Endpoint	N = 62
Hematologic response	
Complete response	77%
Cytogenetic response	
Major response	23%
Complete response	16%

Cortes J et al. *Blood* 2012c;120(13):2573–80.

Track 12

DR LOVE: Let's chat about myelofibrosis (MF). Would you talk about your recent publication in *Blood* (Verstovsek 2012b), which evaluated the long-term outcomes of patients who received ruxolitinib?

DR CORTES: This study evaluated patients with MF who received treatment with ruxolitinib on clinical trials before it was approved. The improvement in the spleen size and in MF symptoms with ruxolitinib has been well established. The question we wanted to address was whether ruxolitinib had an effect on survival compared to matched historical controls. Our study demonstrated a clear improvement in survival for patients who received ruxolitinib (Verstovsek 2012b; [3.5]).

More than 50% of patients were still receiving treatment with ruxolitinib more than 3 years after starting therapy. Most of the patients who respond can maintain their responses. The discontinuation rate due to adverse events was low. That was confirmed by the COMFORT-I study, in which ruxolitinib was compared to placebo (Verstovsek 2012a). In the last analysis of the COMFORT-I study, a small but significant survival benefit with ruxolitinib was noted, which is remarkable given the short follow-up. ■

3.5

Long-Term Outcomes for 107 Patients with Myelofibrosis Receiving Ruxolitinib in Comparison to Matched Historical Controls

Overall survival rate in the high-risk group	Ruxolitinib (n = 63)	Control (n = 165)	HR, *p*-value
One year	95%	81%	HR = 0.5 *p* = 0.006
Two years	83%	58%	
Three years	63%	35%	

- After a median follow-up of 32 months, 54% of patients were still receiving ruxolitinib, with an overall survival of 69%.
- Overall survival among 107 patients who received ruxolitinib was significantly better than that of the 310 matched historical controls ($p = 0.005$).

Verstovsek S et al. *Blood* 2012b;120(6):1202-9.

SELECT PUBLICATIONS

Cortes JE. **Not only response but early response to tyrosine kinase inhibitors in chronic myeloid leukemia.** *J Clin Oncol* 2012a;30(3):223-4.

Cortes J et al. **PACE: A pivotal phase II trial of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation.** *Proc ASCO* 2012b;**Abstract 6503**.

Cortes J et al, on behalf of the Omacetaxine 202 Study Group. **Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation.** *Blood* 2012c;120(13):2573-80.

Jabbour E et al. **Inotuzumab ozogamycin (I0), a CD22 monoclonal antibody conjugated to calecheamicin, given weekly, for refractory-relapse acute lymphocytic leukemia (R-R ALL).** *Proc ASCO* 2012;**Abstract 6501**.

Jain P et al. **Early molecular and cytogenetic responses predicts for significantly longer event free survival and overall survival in patients with newly diagnosed chronic myeloid leukemia in chronic phase — An analysis of 4 tyrosine kinase inhibitor modalities (standard dose imatinib, high dose imatinib, dasatinib and nilotinib).** *Proc ASH* 2012;**Abstract 70**.

Khoury HJ et al. **Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure.** *Blood* 2012;119(15):3403-12.

Marin D et al. **Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors.** *J Clin Oncol* 2012;30(3):232-8.

Topp M et al. **Effect of anti-CD19 BiTE blinatumomab on complete remission rate and overall survival in adult patients with relapsed/refractory B-precursor ALL.** *Proc ASCO* 2012;**Abstract 6500**.

Verstovsek S et al. **A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis.** *N Engl J Med* 2012a;366(9):799-807.

Verstovsek S et al. **Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: Survival advantage in comparison to matched historical controls.** *Blood* 2012b;120(6):1202-9.

INTERVIEW

Lauren C Pinter-Brown, MD

Dr Pinter-Brown is Director of the UCLA Lymphoma Program and Clinical Professor of Medicine at the Geffen School of Medicine at UCLA in Los Angeles, California.

Tracks 1-14

Select Excerpts from the Interview

Track 3

DR LOVE: How do you approach the off-protocol treatment of peripheral T-cell lymphoma (PTCL)?

DR PINTER-BROWN: I am currently using CHOP but substituting etoposide for the doxorubicin. At my institution when a patient has a complete response he or she will receive high-dose chemotherapy and autologous stem cell rescue up front.

We have 2 FDA-approved agents for PTCL — pralatrexate and romidepsin — to use in the relapsed or refractory setting (4.1, 4.2). These are both administered intravenously but belong to totally different classes of drugs.

Pralatrexate is an antifolate and romidepsin is an HDAC inhibitor. So we should see no interference of one drug with another, and if a patient does not respond to one agent,

that should have no implications regarding the chance of response to the other agent. The primary toxicity of pralatrexate is mucositis, and one tries hard to preserve the quality of life (QOL) while at the same time achieving a response.

DR LOVE: What are the side effects of romidepsin, and how are they managed?

DR PINTER-BROWN: The biggest toxicities affect QOL. Patients tend to develop low-grade nausea and fatigue, which can be managed in several ways, such as using antiemetics or ensuring that the patient is well hydrated. Neurostimulatory agents have been used to treat fatigue. In practice, I've administered the drug every other week,

4.1

Results from the Pivotal PROPEL Study of Pralatrexate for Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL)

Response	Pralatrexate (n = 111)
Response rate	29%
Median duration of response	10.1 months
Median progression-free survival	3.5 months
Median overall survival	14.5 months
Select adverse events (Grade ≥3)	
Thrombocytopenia	33%
Mucositis	22%
Neutropenia	22%
Anemia	18%

Conclusion: "To our knowledge, PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) is the largest prospective study conducted in patients with relapsed or refractory PTCL. Pralatrexate induced durable responses in relapsed or refractory PTCL irrespective of age, histologic subtypes, amount of prior therapy, prior methotrexate, and prior autologous stem-cell transplant. These data formed the basis for the US Food and Drug Administration approval of pralatrexate, the first drug approved for this disease."

O'Connor OA et al. *J Clin Oncol* 2011;29(9):1182-9.

4.2

Results from a Pivotal Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) After Prior Systemic Therapy

Response	Romidepsin (n = 130)
Objective response rate	25%
Median duration of response	17 months
Select adverse events (Grade ≥3)	
Thrombocytopenia	24%
Neutropenia	20%
Infections	19%

Conclusion: "Single-agent romidepsin induced complete and durable responses with manageable toxicity in patients with relapsed or refractory PTCL across all major PTCL subtypes, regardless of the number or type of prior therapies. Results led to US Food and Drug Administration approval of romidepsin in this indication."

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

instead of 3 weeks on and 1 week off, because the patients tend to feel quite good on the week off. I've also tried dose reduction.

Tracks 4-5

DR LOVE: Would you discuss the efficacy and safety of everolimus in Hodgkin lymphoma?

DR PINTER-BROWN: I've been extremely impressed with everolimus. I participated in the Phase II trial of this agent in 42 patients with relapsed or refractory Hodgkin lymphoma (Johnston 2012; [4.3]). Some had complete remissions and went on to receive a transplant, and several patients have been on the trial for about 2 years. These are patients for whom ASCT had failed quickly. They have sustained partial responses and a superb QOL with everolimus. I would like to see the data expanded because I believe everolimus could be even more useful than brentuximab vedotin in Hodgkin lymphoma.

Approximately 40% of patients with relapsed or refractory Hodgkin lymphoma who received brentuximab vedotin in a Phase II trial developed peripheral neuropathy (Younes 2012). Although some patients respond, the duration of response to brentuximab vedotin is short. In my experience, many patients develop peripheral neuropathy around the eighth dose and need to stop therapy. If the patient has a complete response, it may be the only therapy needed because complete responses are durable. If the patient has a partial response, I would see it more as a bridge to move rapidly to transplantation. ■

4.3

Everolimus for Relapsed or Refractory Classical Hodgkin Lymphoma in an Open-Label, Single-Arm, Phase II Study

Best overall response	Everolimus (10 mg/d) (N = 42)
Overall response rate Complete response (CR)* Partial response (PR)	38.1% 7.1% 30.95%
Stable disease (SD)	28.6%
Progressive disease	14.3%
Unknown	19.0%

* Defined as resolution of all adenopathy
Disease control rate (CR + PR + SD) = 66.7%

Johnston PB et al. *Proc ASCO* 2012;**Abstract 8028**.

SELECT PUBLICATIONS

Coiffier B et al. **Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.** *J Clin Oncol* 2012;30(6):631-6.

Johnston PB et al. **Everolimus (EVE) for relapsed/refractory classical Hodgkin lymphoma (cHL): Open-label, single-arm, phase II study.** *Proc ASCO* 2012;**Abstract 8028**.

O'Connor OA et al. **Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study.** *J Clin Oncol* 2011;29(9):1182-9.

Younes A et al. **Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma.** *J Clin Oncol* 2012;30(18):2183-9.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The RESORT trial indicated that rituximab re-treatment upon disease progression was equally as effective as rituximab maintenance therapy with regard to time to treatment failure among patients with low tumor burden FL.**
   a. True
   b. False

2. **The ECOG-E1411 study will randomly assign patients with MCL to either BR or bendamustine/bortezomib/rituximab as induction therapy followed by rituximab alone or _____.**
   a. Interferon alpha
   b. Watch and wait
   c. Lenalidomide and rituximab

3. **In a trial of R-FC versus R-CHOP followed by maintenance therapy with rituximab or interferon alpha among elderly patients with MCL, R-CHOP and rituximab maintenance yielded the greatest benefit in terms of duration of response and survival.**
   a. True
   b. False

4. **In a Phase I/II trial, carfilzomib in combination with lenalidomide and low-dose dexamethasone as front-line therapy for patients with newly diagnosed multiple myeloma generated high response rates but was associated with which of the following side effects?**
   a. Hyperglycemia
   b. Fatigue
   c. Muscle cramping
   d. Thrombocytopenia
   e. All of the above

5. **_____, a monoclonal antibody that is directed at the cell surface glycoprotein CD38, has reported single-agent activity in patients with relapsed or refractory multiple myeloma.**
   a. Elotuzumab
   b. Daratumumab
   c. Neither of the above

6. **A recent ASCO presentation demonstrated responses in patients who underwent treatment with the immunoconjugate inotuzumab ozogamicin for relapsed or refractory ALL.**
   a. True
   b. False

7. **Patients with CML who experience an early response to TKI therapy at 3 months are more likely to have a better long-term outcome.**
   a. True
   b. False

8. **Which of the following is an approved treatment for CML?**
   a. Dasatinib
   b. Imatinib
   c. Nilotinib
   d. Omacetaxine
   e. Bosutinib
   f. Ponatinib
   g. All of the above

9. **Long-term follow-up of patients with MF treated with ruxolitinib did not demonstrate a significant survival advantage with ruxolitinib compared to historically matched controls.**
   a. True
   b. False

10. **Pralatrexate and romidepsin are both administered intravenously and both act by inhibiting histone deacetylase (HDAC).**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 2012

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 1 — 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
Activity of novel agents blinatumomab and inotuzumab ozogamicin in relapsed or refractory ALL	4 3 2 1	4 3 2 1
Efficacy, toxicity, dose and duration of treatment with the JAK2 inhibitor ruxolitinib in MF	4 3 2 1	4 3 2 1
Incidence of peripheral neuropathy associated with the use of carfilzomib in multiple myeloma	4 3 2 1	4 3 2 1
Newly approved therapeutic options for patients with relapsed or refractory CML	4 3 2 1	4 3 2 1
Activity of everolimus in relapsed or refractory Hodgkin lymphoma	4 3 2 1	4 3 2 1
Survival benefit with rituximab versus interferon as maintenance therapy after R-CHOP in elderly patients with 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
☐ 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:

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of approved first- and second-generation tyrosine kinase inhibitors and protein translation inhibitors as therapeutic options for patients with chronic myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Develop an understanding of emerging efficacy and side-effect data with JAK2 inhibitors in myelofibrosis in order to inform patients regarding protocol and nonprotocol treatment options. . . . . 4 3 2 1 N/M N/A
- Counsel patients with follicular and mantle-cell lymphoma about recent advances in induction and maintenance systemic treatment, and integrate these advances into current treatment algorithms as appropriate. . . . . 4 3 2 1 N/M N/A
- Describe the biologic rationale for and emerging roles of novel and approved antibody-drug conjugates — alone and in combination with chemotherapy — in the treatment of Hodgkin lymphoma, acute lymphoblastic leukemia and other CD30- or CD22-positive hematologic disorders. . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

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.

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

PART 2 — 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
Michael E Williams, MD, ScM	4 3 2 1	4 3 2 1
P Leif Bergsagel, MD	4 3 2 1	4 3 2 1
Jorge E Cortes, MD	4 3 2 1	4 3 2 1
Lauren C Pinter-Brown, 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:

.....

.....

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