Ongoing Phase III Ro-CHOP Trial of CHOP versus Romidepsin-CHOP for Patients with Previously Untreated Peripheral T-Cell Lymphoma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) annual meeting and the International Conference on Malignant Lymphoma (ICML), to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important ongoing trials and emerging data sets on novel agents in T-cell lymphoma from the latest ASCO and ICML meetings, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate emerging efficacy and safety data with the anti-CD30 agent brentuximab vedotin and the novel histone deacetylase inhibitor belinostat as therapy for patients with relapsed or refractory T-cell lymphoma.
- Demonstrate knowledge of currently recruiting trials of the targeted agents brentuximab vedotin, belinostat and romidepsin as single agents or in combination with chemotherapy, and counsel appropriate patients with T-cell lymphoma for participation in these ongoing trials.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc and
Spectrum Pharmaceuticals Inc.
Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari
3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio
Last review date: October 2013
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One of the best examples of the recent transformation of clinical and translational science in the many variants of T-cell lymphoma (TCL) was a case presented by Dr Andrew Evens during a lymphoma think tank we hosted this summer in our Miami recording studio.

This 61-year-old man was diagnosed 2 years ago with Stage IV ALK-negative anaplastic large-cell lymphoma (ALCL) and received CHOEP — a common up-front choice among investigators — which resulted in a complete response (CR). Like many patients with peripheral T-cell lymphoma (PTCL) who hear the pros and cons of various forms of transplant, the patient balked at taking that difficult step and was followed expectantly for a year, when an obvious and significant recurrence was detected. Until recently this man’s treatment options would have been confined to intensive salvage chemotherapy regimens, like ICE, DHAP and ESHAP, and other less intense options, including romidepsin, pralatrexate and other agents, but in 2013 we know that ALCL is uniformly CD30-positive and, as with about 60% of individuals with this disease who receive the antibody-drug conjugate (ADC) brentuximab vedotin (BV), this patient experienced a rapid CR and no significant toxicity. He then reconsidered his decision and elected to receive an autologous stem cell transplant and remains in CR 6 months later.

Unlike many other corners of oncology, including B-cell lymphomas, for which novel agents and strategies abound, TCL has until recently been devoid of these hopeful entities and the unfortunate result is painfully evident in a recent JCO paper. This retrospective study of 153 patients in British Columbia who underwent treatment for PTCL (mostly PTCL NOS, angioimmunoblastic TCL [AITL] or ALCL) from 1976 to 2010 demonstrated a dismal median time from diagnosis to first relapse of 6.7 months and an even worse 5.5 months from first relapse to death. However, as seen with Dr Evens’ patient, critical inroads have now been made, and equally as important, an effective clinical research infrastructure has emerged that is generating well-designed and executed studies. The ASCO and Lugano TCL papers summarized on this issue of 5-Minute Journal Club typify recent steps forward and shine a light on where we might be in a few years.
1. **Belinostat: The BELIEF Phase II trial**

The big T-cell story out of ASCO was this report of significant single-agent activity with a 26% response rate with this novel pan-histone deacetylase inhibitor (HDACi) in patients with relapsed/refractory (R/R) PTCL. Although on the surface some might review the data and think this is just another HDACi, during a recent interview for our audio series BELIEF principal investigator Dr Owen O’Connor discussed the potential game-changing difference of this drug. Specifically, unlike other agents with significant activity in PTCL, including romidepsin, the rate of myelosuppression is relatively low with belinostat and as such it can be administered to patients with platelet counts above 50,000.

From a clinical perspective this unique attribute may prove invaluable in the R/R setting, in which many patients have poor marrow reserve because of prior chemotherapy and in some cases transplant. Similarly, in terms of clinical research belinostat may be safer and easier to combine with chemotherapy, potentially allowing for more effective drug delivery — a strategy now being tested in up-front trials. The news did not stop at ASCO, as in Lugano Dr Steven Horwitz presented further data from BELIEF demonstrating that patients with AITL were particularly likely to benefit from the drug (46% response rate). These data have led many to become “believers” that belinostat may have real value and perhaps a role soon in clinical practice.

2. **CD30 and BV**

We’ve talked a lot about this fascinating ADC in past programs, but the database continues to build and at Lugano we saw an interesting report from a Phase II US trial of 29 patients with mature T-/NK-cell lymphomas. Importantly, of 17 patients with postbaseline assessments, all but 3 experienced tumor size decreases and CRs were observed in 4 of 10 patients with AITL and 2 of 12 patients with PTCL NOS. These and prior data sets suggest that clinicians might want to consider CD30 testing for all patients with PTCL and maybe some B-cell cancers like diffuse large B-cell lymphoma along with cutaneous TCL, in which an ongoing Phase III trial is evaluating the efficacy of BV and anecdotal benefit has been observed. Interestingly, the correlation between CD30 status and response to BV is not as clear as one might think, and this paper like others before it reports durable responses in patients with low or undetectable CD30 expression.

Last week in the Big Apple during the first of our 4 daylong regional Year in Review (YIR) symposia, Dr Bruce Cheson commented on the challenge of using this marker and cited the example of Hodgkin lymphoma, in which most cells in the tumor mass are stroma and are CD30-negative but virtually all Reed-Sternberg cells have the antigen, thus explaining the impressive clinical activity in these patients. Another YIR faculty member, Dr Lauren Pinter-Brown, commented on 2 other factors confounding current CD30 evaluation, namely tumor heterogeneity and the evolution of newer, more sensitive assays, including quantitative image analysis, that may be able to identify
many more patients than the estimated 30% with PTCL currently considered to have CD30-positive tumors. Where this leads in the future is uncertain, but it’s possible that BV and other ADCs will eventually be utilized in most patients with TCL.

3. **The next generation of TCL clinical trials**

Despite the many advances in TCL treatment, continued research is of course needed, and at ASCO Dr O’Connor presented a Trials in Progress poster (TPS) featuring the newly launched and much anticipated Phase III ECHELON-2 study. This critical effort compares up-front CHOP to CHBVP, in which BV replaces vincristine in the front-line treatment of patients with CD30-positive mature TCLs, and should be widely embraced by clinicians who otherwise must turn to suboptimal standard options. In a similar manner, another relevant ASCO TPS focused on the Phase III RoCHOP trial, which adds the HDACi romidepsin to CHOP in patients with previously untreated PTCL. In terms of new agents, Dr Anas Younes, the new Chief of the Memorial Sloan-Kettering Lymphoma Service, in a brilliant ASCO review of many exciting ADCs in development said it’s “prime time” for these agents in lymphoid cancers. He then underscored the immense value of this therapeutic concept by noting the important example of ALCL, where the unconjugated anti-CD30 antibody produced a 17% response rate that increased to 86% when the same naked antibody was conjugated to monomethyl auristatin E (MMAE).

Many other novel agents and strategies are being actively investigated in TCL, and Dr Pinter-Brown told our highly attentive and knowledgeable New York audience that TCL needs a “rituximab.” In that regard, she is intrigued by mogamulizumab, a defucosylated humanized monoclonal antibody targeting C-C chemokine receptor 4 (CCR4) that is approved in Japan for R/R adult T-cell leukemia/lymphoma and is currently working its way through trials in North America, where the face of this disease is considerably different.

Next, for our final issue of this series on summer heme-onc data sets we flip back to the “B” side and check out papers on follicular, mantle-cell and diffuse large B-cell lymphoma.

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Ongoing Phase III Ro-CHOP Trial of CHOP versus Romidepsin-CHOP for Patients with Previously Untreated Peripheral T-Cell Lymphoma

Presentations discussed in this issue

Delarue R et al. ROCHOP study: A Phase III randomized study of CHOP compared to romidepsin-CHOP in untreated peripheral T-cell lymphoma. Proc ASCO 2013; Abstract TPS8616.

Delarue R et al. ROCHOP study: A Phase III randomized study of CHOP compared to romidepsin-CHOP in untreated peripheral T-cell lymphoma. Proc ICML 2013; Abstract 564.

Slides from presentations at ASCO 2013 and ICML 2013 and transcribed comments from a recent interview with Julie M Vose, MD, MBA (7/19/13)
Background

- Peripheral T-cell lymphoma (PTCL) is an aggressive disease that accounts for about 15% of non-Hodgkin lymphoma and is associated with poor prognosis even with up-front CHOP therapy.
- A pivotal Phase II trial of romidepsin, a histone deacetylase inhibitor, showed a response rate of 25% among patients with heavily pretreated PTCL (JCO 2012;30:631).
  - Patients (15%) achieved a CR/Cru.
  - Of those who achieved CR/CrU, 89% were without disease progression at a median follow-up of 13.4 months.
- In the Phase Ib part of the Ro-CHOP study, the recommended dose for romidepsin was 12 mg/m² on days 1 and 8 of each cycle (Proc ASH 2012;Abstract 1617).
- **Study objective:** To compare the efficacy and safety of romidepsin/CHOP versus CHOP in previously untreated PTCL.


Ongoing Phase III Ro-CHOP Trial Design (NCT01796002)

**Target accrual (n = 420)**
- Previously untreated PTCL*
- Ann Arbor Stage I-IV
- Age: 18-80 years

Study start date: January 2013
Estimated study completion date: July 2022

**Romidepsin + CHOP**
- 6 cycles or until PD

**CHOP**
- 6 cycles

* Includes PTCL not otherwise specified (PTCL-NOS); angioimmunoblastic T-cell lymphoma; ALK-negative anaplastic large cell lymphoma (ALCL); enteropathy-associated T-cell lymphoma; hepato-splenic T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma

- **Primary endpoint:** Progression-free survival (PFS) by independent review
- **Secondary endpoints include:** Overall survival, response rate, duration of response, safety and quality of life

Study Methods

- Patients will be stratified prior to randomization by:
  - International Prognostic Index (IPI) score (<2 vs ≥2)
  - Age (≤60 vs >60 years)
  - Investigator-assessed histology (nodal vs extranodal)
- A recruitment of 10.5 patients per month is anticipated, with a total duration of the study of 60 months.
- Romidepsin (IV) will be administered before CHOP on days 1 and 8 of each 3-week cycle:
  - Starting dose: 12 mg/m²
  - Dose adaptations (2 levels: 10 and 8 mg/m²) according to toxicities (neutropenia, thrombocytopenia, cardiac toxicity)
- CHOP will be administered in 3-week cycles.


Concomitant Treatments

- Concomitant treatments allowed on the study include:
  - Prophylaxis for tumor lysis syndrome prior to cycle 1 or for Pneumocystis jirovecii infection
  - Primary prophylaxis with G-CSF — mandatory
  - Antiemetics prior to CHOP or romidepsin administration
  - Serum potassium or magnesium before each dose of romidepsin; low levels must be corrected, orally or by IV, prior to romidepsin administration
- Prohibited concomitant treatments include:
  - Steroids other than those specified in the study protocol
  - Use of drugs that cause prolongation of QTc
  - Use of strong CYP3A4 inhibitors or potent inducers
  - Use of therapeutic warfarin

Measurement of Endpoints

- All responses will be assessed by central review.
- CT scans will occur at study entry, after cycle 3, at the end of treatment, every 3 months during the first 2 years and then every 6 months.
- Central review will occur in real time of all suspected progression during the treatment and follow-up study phases.
- $^{18}$FDG-PET scan (not mandatory) may be performed at study entry and at the end of treatment.
- There will be a central review of all pathological samples at disease diagnosis and relapse.
- Quality of life will be assessed using the EORTC QLQC-30 questionnaire.


Exploratory Objectives

- Evaluation of response rate by FDG-PET scan assessment
- Concordance between investigator-assessed and centrally reviewed efficacy data
- Association between biological profile in tumor sample and the efficacy of romidepsin

Investigator Commentary: The Phase III Ro-CHOP Trial of Romidepsin/CHOP versus CHOP in Previously Untreated PTCL

This is a follow-up Phase III study to a Phase II study that was presented at the 2013 12th International Conference on Malignant Lymphoma in Lugano that combined romidepsin with CHOP. The results of the Phase II study were somewhat disappointing in that the response rates did not appear to be much higher than what would be expected with CHOP alone, and the toxicity was substantial. I’m unsure as to what the results of the Phase III trial will be, but I believe the toxicity issue will be apparent in this trial also. I would like to see us get away from using CHOP, but I don’t know that we have the data yet to say that we can.

*Interview with Julie M Vose, MD, MBA, July 19, 2013*