INTERVIEW

Owen A O'Connor, MD, PhD

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Tracks 1-10

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss the treatment options for patients with relapsed/refractory CD30-negative peripheral T-cell lymphoma (TCL)?

DR O'CONNOR: In my practice, we tend to use the FDA-approved single agents, pralatrexate and romidepsin, for patients with relapsed or refractory peripheral TCL. Evaluation of the data reveals that romidepsin and pralatrexate are able to achieve substantial remissions in many patients.

In the PROPEL trial evaluating pralatrexate for relapsed or refractory peripheral TCL, patients had received a median of 3 prior lines of therapy (O'Connor 2011). For patients who received pralatrexate after their first relapse, the response rate was higher than the response rate for the entire study population. Because these diseases generally perform poorly with combination therapy, I tend to consider these new agents earlier.

DR LOVE: How do you choose between romidepsin and pralatrexate?

DR O'CONNOR: In my experience, pralatrexate works faster than romidepsin. I would administer pralatrexate first if I had a sense that a patient had a lot of disease-related symptoms and required disease control, assuming the patient was not malnourished. For those with small-volume disease with a good performance status, we administer romidepsin because it requires more time to provide benefit.

DR LOVE: What has been your clinical experience with the toxicity of pralatrexate and romidepsin?

DR O'CONNOR: With pralatrexate, the big issue is mucositis. The incidence of Grade 3/4 mucositis in the PROPEL study was 22%. If a patient develops even low-grade mucositis, we treat it early with leucovorin between the intervening doses of pralatrexate, which seems to have a big effect on lowering its incidence. Also, we may start pralatrexate at a lower dose and gradually escalate. Another side effect of pralatrexate is thrombocytopenia. Romidepsin is well tolerated with durable responses, but like most HDAC inhibitors it has side effects including fatigue, anorexia and thrombocytopenia. If I have a patient who is a little older who I don't believe would be able to tolerate the potential mucositis with pralatrexate, I will consider administering romidepsin first in that scenario.

Track 6

DR LOVE: What is the rationale for trials evaluating the integration of up-front pralatrexate and romidepsin in TCL?

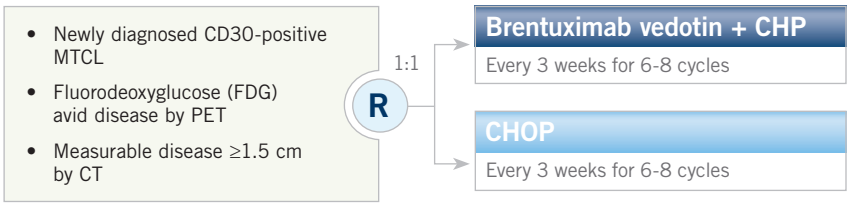
DR O'CONNOR: Our independent review board recently approved a Phase I/II study that will investigate the combination of pralatrexate with romidepsin in the up-front setting. The rationale is based on our laboratory data with preclinical murine models of TCL. This will be the first trial to evaluate combining these active T-cell-specific agents to try to build new platforms that could challenge CHOP as an up-front regimen.

DR LOVE: Continuing with the concept of trials of up-front treatment, would you discuss the ongoing Phase III ECHELON-2 trial for patients with newly diagnosed mature TCL (MTCL)?

1.1

ECHELON-2: An Ongoing Phase III Trial of Brentuximab Vedotin/CHP versus CHOP Chemotherapy in the Front-Line Treatment of CD30-Positive Mature T-Cell Lymphoma (MTCL)

Target Accrual: n = 300



Primary endpoint: Progression-free survival by independent review

CHP = cyclophosphamide/doxorubicin/prednisone

O'Connor OA et al. *Proc ASCO* 2013;**Abstract TPS8611**.

DR O'CONNOR: The ECHELON-2 trial is an important registration-directed study of brentuximab vedotin/CHP versus CHOP in MTCL (O'Connor 2013; [1.1]). Because it is only for MTCL, it will account for approximately one third of patients with TCL. If the activity of brentuximab vedotin/CHP is anywhere close to what we've observed in anaplastic large cell lymphoma and the early signals that we see in TCL and diffuse large B-cell lymphoma, this may represent one of the first big advances to a CHP backbone by adding a new agent that could advance the up-front induction care for these patients.

Other randomized Phase III trials in peripheral TCL are evaluating pralatrexate or romidepsin with CHOP (1.2). This makes 3 international studies in the up-front setting for patients with TCL.

1.2

Select Ongoing Phase III Clinical Trials of Romidepsin and Pralatrexate for Patients with Peripheral T-Cell Lymphoma

Trial ID	N	Treatment arms
NCT01796002 (Ro-CHOP)	420	• Romidepsin + CHOP • CHOP
NCT01420679	549	• CHOP-based CT → pralatrexate • CHOP-based CT → observation

CT = chemotherapy

www.clinicaltrials.gov, October 2013.

Tracks 7-8

DR LOVE: Would you discuss the results of the Phase II BELIEF trial?

DR O'CONNOR: The BELIEF trial evaluated a new HDAC inhibitor, belinostat, in relapsed or refractory PTCL and reported a response rate of approximately 26% (O'Connor 2013; [1.3]). The duration of response and much of the BELIEF trial results are similar to what we've observed with the other HDAC inhibitors. It's difficult to compare it to vorinostat because we have little to no experience with vorinostat in PTCL.

Of note, the BELIEF trial reaffirmed that HDAC inhibitors have a unique class effect in TCL, with activity of 25% to 30%. One of the interesting observations of the BELIEF trial was the activity in patients with low platelet counts. More important, belinostat was well tolerated irrespective of the baseline platelet count.

DR LOVE: What are your thoughts on the results of the subset analysis of the BELIEF trial in patients with angioimmunoblastic T-cell lymphoma (AITL)?

DR O'CONNOR: An interesting observation from the BELIEF study was the response rate in AITL (Horwitz 2013; [1.3]). This was higher than previously reported in the PROPEL study with pralatrexate. With belinostat, the response rate in AITL was markedly higher than what was reported in the overall patient population. That was taken as a signal that some interesting biology may be targeted by belinostat in patients with the AITL subtype that is not targeted by the other HDAC inhibitors. This is a provocative finding, but we need more data.

1.3

Efficacy and Safety Results from the Phase II BELIEF Trial of Single-Agent Belinostat, a Novel Pan-HDAC Inhibitor, for Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

Outcome	All patients* (n = 120)	AITL† (n = 22)	Baseline platelet counts*	
			≥100,000/uL	<100,000/uL
ORR	25.8%	46%	28%	15.0%
Median DoR	13.6 months	NR	13.6 months	4.1 months
Median PFS	1.6 months	4.2 months	1.8 months	1.3 months
Median OS	7.9 months	NR	9.2 months	4.3 months
Median TTR	5.6 weeks	NR	5.6 weeks	6.4 weeks
Grade ≥3 AEs	(n = 129)	(n = 22)	(n = 105)	(n = 24)
Thrombocytopenia	15%	23%	6%	54%
Neutropenia	13%	9%	10%	25%
Leukopenia	13%	9%	9%	29%
Anemia	12%	27%	8%	29%
Dyspnea	6%	NR	NR	NR
Pneumonia	6%	NR	NR	NR

AITL = angioimmunoblastic T-cell lymphoma; ORR = overall response rate; DoR = duration of response; NR = not reported; PFS = progression-free survival; OS = overall survival; TTR = time to response; AEs = adverse events

* O'Connor OA et al. *Proc ASCO* 2013;**Abstract 8507**; † Horwitz S et al. *Proc ICML* 2013;**Abstract 153**.

Track 10

DR LOVE: In light of the recent FDA approval of lenalidomide for relapsed or progressive mantle-cell lymphoma (MCL), how do you sequence lenalidomide and bortezomib?

DR O'CONNOR: I've seen bortezomib work remarkably well in patients with chemotherapy-resistant MCL. When combined with alkylating agents such as cyclophosphamide or bendamustine, it converts chemotherapy-resistant or refractory disease to chemotherapy-sensitive disease. So bortezomib can help overcome acquired and intrinsic drug resistance by its integration even into previously used chemotherapy regimens.

My bias has been that we'll probably try up-front lenalidomide for most patients provided they have no urgent need for rapid cytoreduction. MCL has been managed with lenalidomide-based regimens for several years. I've seen elderly patients ineligible for combination chemotherapy receive lenalidomide-based therapy and achieve sustained complete responses. ■

SELECT PUBLICATIONS

Horwitz S et al. **Belinostat in angioimmunoblastic T-cell lymphoma: Results from the pivotal BELIEF trial.** *Proc ICML* 2013;**Abstract 153**.

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.