5 Minute JournalClub

Key ASH Presentations
Issue 5, 2011

Activity and Safety of Pralatrexate and Romidepsin in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma (PTCL)

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVES

- Counsel patients with PTCL who have previously received ICE-based therapy about the benefits and risks of further treatment with pralatrexate.
- Describe the mechanism of action of romidepsin, and recall the efficacy and safety of this agent for patients with relapsed or refractory PTCL.

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Consulting Agreements: Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company; Paid Research: Allos Therapeutics, Genzyme Corporation.

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Click here for papers on T-cell lymphomas.

Although there are seemingly a multitude of different subtypes, peripheral T-cell lymphomas (PTCL) comprise only about 10 percent of all NHL cases. The related variants of cutaneous T-cell lymphoma (CTCL) are even less common. Nonetheless, in recent years an extraordinary effort by clinical and laboratory investigators has greatly expanded our understanding of the complex biology of these cancers and defined a number of new targets for intervention. In this issue of *5-Minute Journal Club* we profile a handful of new reports in a field that has become a model for research in uncommon, potentially lethal diseases.

1. PTCL papers

Molecularly heterogeneous and with relatively poor long-term outcomes with anthracycline-based chemotherapy, PTCL NOS (not otherwise specified) has been in need of more effective therapies for quite some time. Fortunately, several important advances are beginning to change this discouraging situation. Most recently at ASH, Bertrand Coiffier presented findings from a Phase II trial of 131 patients with PTCL treated with the histone deacetylase (HDAC) inhibitor romidepsin demonstrating a 26 percent objective response rate, with half of these CRs. This report and others have generated enthusiasm that this agent — already approved in CTCL — has important clinical activity in PTCL as well.

A second ASH data set focused on another recently FDA-approved agent for T-cell lymphoma, the targeted antifolate pralatrexate. At ASH we saw the subanalysis from the Phase II PROPEL trial specifically focused on patients with disease progression despite prior treatment with ICE (ifosfamide, carboplatin and etoposide). Eight of 20 patients (40 percent) treated with pralatrexate had an objective tumor response. One of the most common side effects observed with this agent in the trial was mucositis, but weekly scheduling and the concomitant use of folate and vitamin B12 can help mitigate this problem.

2. Anaplastic large cell lymphoma (ALCL)

This intriguing disease has a very different outlook depending on ALK status, as ALK-positive ALCL responds well to anthracycline-based chemotherapy but the ALK-negative variant does not. The good news at ASH relates to the anti-CD30 immune conjugate brentuximab vedotin. As in the related Hodgkin lymphoma (HL) presentation described in a recent issue of this series, the waterfall plot from the **Phase II study in ALCL** was impressive as 56 of the 58 patients (97 percent) with mostly ALK-negative tumors

treated on the trial experienced reductions in tumor size. The CR rate was 53 percent, the PR rate was 33 percent and at the point of follow-up the median response duration had not been reached. Unlike HL, in which minimal activity has been observed with the "naked antibody," in ALCL it has a substantial antitumor effect. However, the exact mechanism of action of the immune conjugate remains to be defined. Because B vedotin is relatively well tolerated, discussions are ongoing about trials evaluating maintenance treatment.

3. CTCL papers

In an interesting poster, Madeleine Duvic reported on a series of 20 patients with CD25-positive CTCL who were re-treated with denileukin diftitox (DD) — a bioengineered protein combining interleukin-2 and diphtheria toxin — after having responded to this agent earlier on a clinical trial and then relapsing. In this series, eight patients (40 percent) experienced an objective response, an important observation suggesting that the presence of anti-DD neutralizing antibodies generated during prior treatment does not preclude further response. Adverse events were mild to moderate, and there were no instances of the much-dreaded capillary leak syndrome that is now uncommon with the preemptive use of corticosteroids.

Finally, Steve Horwitz reported a study employing a dose deescalation design to attempt to find an active but lower dose/regimen of pralatrexate in CTCL that would allow for continuous or maintenance treatment of this generally indolent disease. Steve's findings show that using 15 mg/m^2 for three out of four weeks was effective and worthy of additional study.

Next up on this ASH highlights series: New agents and regimens in mantle-cell and diffuse large B-cell lymphoma.

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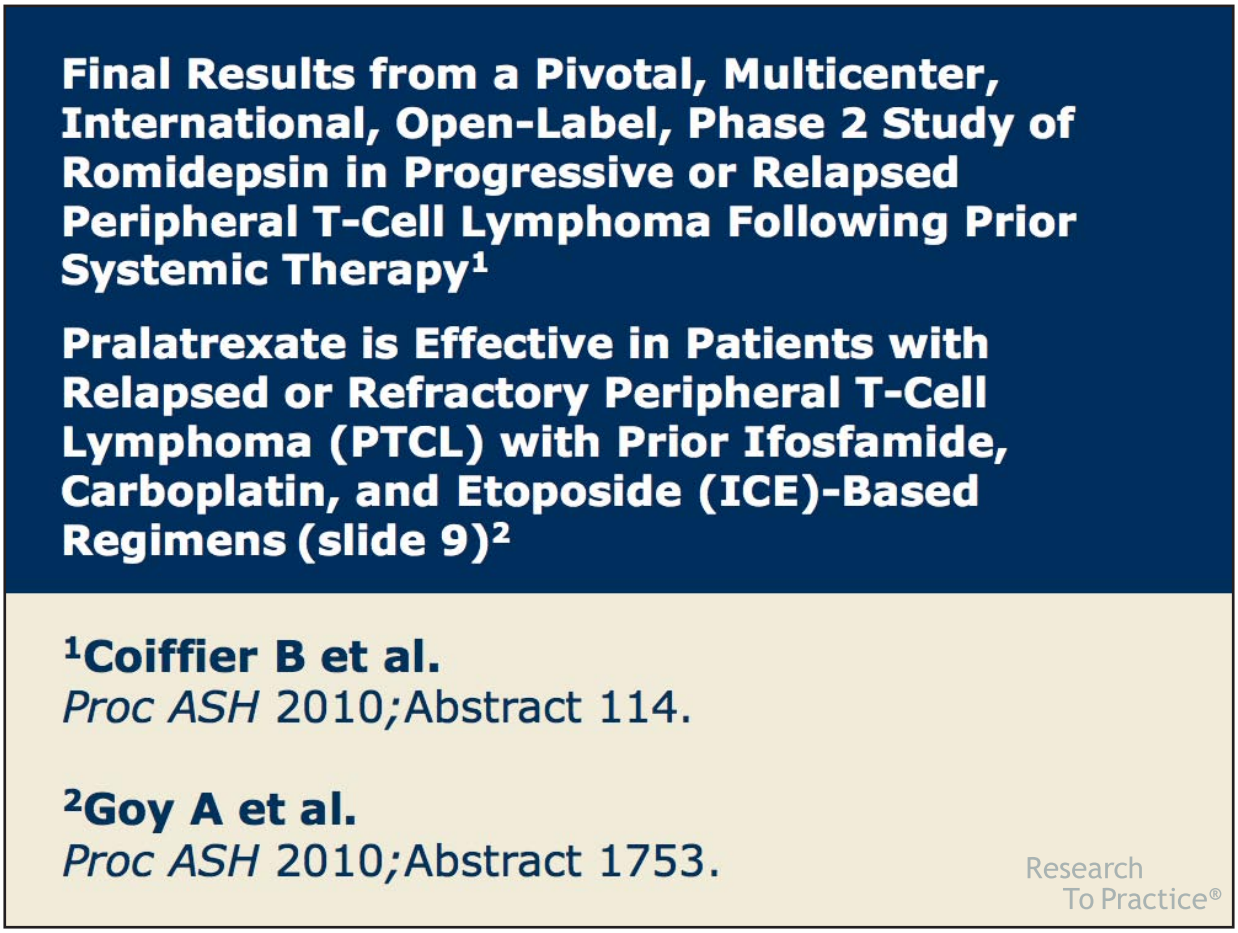
Activity and Safety of Pralatrexate and Romidepsin in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma (PTCL)

Presentations discussed in this issue

Coiffier B et al. **Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma following prior systemic therapy.** *Proc ASH* 2010;**Abstract 114**.

Goy A et al. **Pralatrexate is effective in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with prior ifosfamide, carboplatin and etoposide (ICE)-based regimens.** *Proc ASH* 2010;**Abstract 1753**.

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Steven M Horwitz, MD (12/29/10)



Final Results from a Pivotal, Multicenter, International, Open-Label, Phase 2 Study of Romidepsin in Progressive or Relapsed Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

Coiffier B et al.

Proc ASH 2010;Abstract 114.

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Background

- Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of non-Hodgkin's lymphoma.
  - Aggressive clinical behavior
  - Poor response to chemotherapy
  - High relapse rate
  - Poor long-term survival
- Romidepsin is a histone deacetylase (HDAC) inhibitor, currently approved for patients with cutaneous T-cell lymphoma (CTCL) who have received at least one prior systemic therapy.

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

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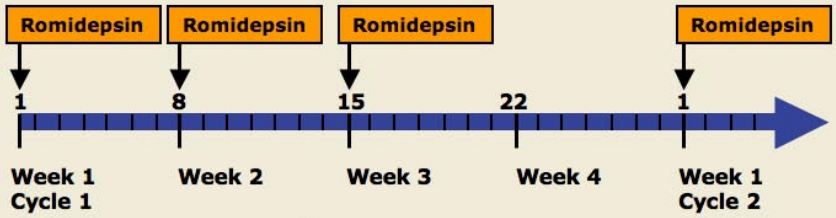
Study Schema

Eligibility (n = 131)
Confirmed PTCL
Failed at least one prior systemic therapy
Measurable disease
Primary endpoint: Complete response by Independent Review Committee



Romidepsin 14 mg/m^2 IV over 4 hours
Days 1, 8 and 15 of a 28-day cycle x 6 cycles
Responding patients could continue to receive treatment beyond 6 cycles at discretion of patient and investigator

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

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Efficacy Outcomes

Efficacy Outcomes (n = 130)	Independent Review Committee (IRC) Assessment	Investigator's Assessment
Objective response rate (ORR)	26%	29%
Duration of objective response (median)	12 months	12 months
Time to objective response	2 months	2 months
Complete response (CR/CRu) CR CRu	13% 8% 5%	16% 14% 2%
Duration of complete response (median)	Not reached	14 months
Partial response	13%	13%

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

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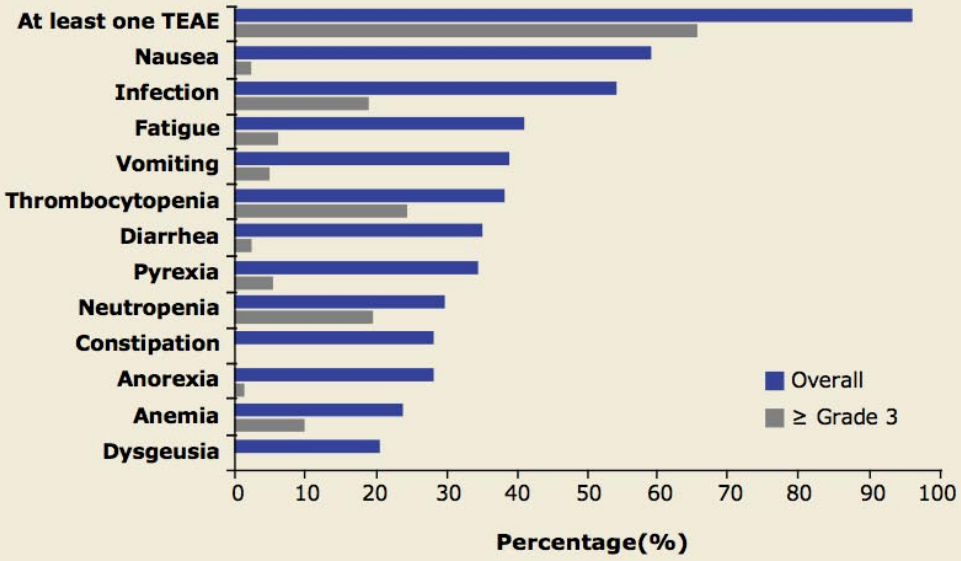
Treatment-Emergent Adverse Events (TEAEs)



With permission from Coiffier B et al. *Proc ASH* 2010;Abstract 114.

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Author Conclusions

- Significant activity demonstrated with single-agent romidepsin in relapsed/refractory PTCL.
  - ORR = 26% (IRC), 29% (Investigator)
  - Median duration of response = 12 mos (IRC and Investigator)
- Rate of CR/CRu = 13% (IRC), 16% (Investigator)
  - Median duration of response = Not reached (IRC), 14 mos (Investigator)
- Responses reported across all major PTCL subtypes (data not shown).
- Single-agent romidepsin therapy was generally well tolerated with manageable toxicities.

Coiffier B et al. *Proc ASH* 2010;Abstract 114.

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Investigator comment on romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL)

This is a relatively large Phase II study of romidepsin in relapsed/refractory PTCL, and it enrolled almost all subtypes. A central review of pathology was conducted, and responses were also centrally assessed. The real highlight of these data is an independently assessed CR rate of 13 percent, which is high, and the duration of response is also quite good. The drug might be approved for PTCL in the relapsed setting. Also, because there does not appear to be any cumulative toxicity, we might be able to use it in a maintenance fashion in the future.

Comparing the data to those with pralatrexate, an approved drug for relapsed/refractory PTCL, the efficacy seems similar though the toxicities are different. The main toxicity of pralatrexate is mucositis, while the toxicities associated with romidepsin are nausea, vomiting and fatigue. I believe no compelling reason exists to prefer one over the other, and like pralatrexate, investigators will try to figure out a way to incorporate romidepsin into earlier lines of therapy.

Interview with Steven M Horwitz, MD, December 29, 2010

Pralatrexate is Effective in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) with Prior Ifosfamide, Carboplatin, and Etoposide (ICE)-Based Regimens

Goy A et al.

Proc ASH 2010;Abstract 1753.

PROPEL Study Schema

Accrual = 109 (Closed)

Eligibility
Confirmed PTCL Documented progression after at least one prior therapy

Primary Endpoint:
Response rate

Secondary Endpoints:
Duration of response (DOR)
Progression-free survival (PFS)
Overall survival (OS)

Pralatrexate 30 mg/m^2 IV push over 3-5 minutes
Weekly administration x 6 weeks of 7-week cycles
with concurrent vitamin B12, 1 mg IM q 8-10 wks
and folic acid, 1.0-1.25 mg po qd

Current exploratory analysis objective:
To assess efficacy and safety in a subset of patients in the PROPEL study who received pralatrexate after failure of ICE-based regimens

ClinicalTrials.gov Identifier NCT00364923
Goy A et al. *Proc ASH* 2010;Abstract 1753.

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Efficacy of Pralatrexate in Patients Who Received Prior ICE-Based Regimens

Efficacy Outcomes (n = 20)	Independent Central Review	Investigator Assessment
Objective Response	40%	40%
Median DOR	13.1 months	16.2 months
Complete Response	15%	25%
Partial Response	25%	15%
Median PFS	14.4 months	4.8 months
Median OS	12.0 months	

Goy A et al. *Proc ASH* 2010;Abstract 1753.

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Efficacy Comparison of Pralatrexate with Prior ICE-Based Regimen Outcomes

Efficacy Outcomes (n = 20)	Patient Responses to Pralatrexate (Independent Central Review)	Patient Responses to Prior ICE-Based Regimens
Objective Response	40%	25%
Complete Response	15%	15%
Partial Response	25%	10%
Median DOR	13.1 months	<1 month

Goy A et al. *Proc ASH* 2010;Abstract 1753.

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Select Adverse Events (AEs)

Grade 3 or 4 AEs ≥5%	Incidence
Anemia	45%
Thrombocytopenia	40%
Mucosal inflammation	30%
Fatigue	5%
Cough	5%
Diarrhea	5%

Goy A et al. *Proc ASH* 2010;Abstract 1753.

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Author Conclusions

- Pralatrexate was active in patients with PTCL who received prior ICE-based chemotherapy.
  - Objective response rate = 40%, including CRs leading to stem cell transplant in two patients
- Single-agent pralatrexate safety profile and outpatient administration appear to compare favorably with ICE-based regimens, which typically require hospitalization for administration.
- Pralatrexate can reverse the characteristic progressive resistance of PTCL and is an effective second-line treatment for patients with PTCL.

Goy A et al. *Proc ASH* 2010;Abstract 1753.

Investigator comment on pralatrexate in relapsed or refractory PTCL previously treated with ICE-based regimens

Pralatrexate is definitely active in this subset of patients, and on face value, it appears that patients who received pralatrexate had a higher response rate and a longer duration of response than they achieved with prior ICE-based regimens. At our institution, the response rate with ICE is much higher and approximately 70 percent, so maybe the PROPEL study was selecting for a group of patients in whom ICE was particularly ineffective. The other issue is that ICE is usually administered for a limited number of cycles because of cumulative toxicity, and pralatrexate in this study was administered until progression. In view of this, I don't believe that comparing the duration of response to the two regimens is fair.

Overall, I believe that the conclusion is a little bit exaggerated that pralatrexate reverses the progressive resistance of patients with T-cell lymphoma to second-line chemotherapy. However, I also believe that these data definitely suggest that pralatrexate is active in patients who are refractory to ICE-based regimens and can be used.

Interview with Steven M Horwitz, MD, December 29, 2010