5 Minute JournalClub

Key ASH Presentations
Issue 5, 2011

Activity of Denileukin Diftitox and Pralatrexate in Relapsed/Refractory Cutaneous T-Cell Lymphoma (CTCL)

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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

- Assess the safety and efficacy of denileukin diftitox re-treatment for patients with relapsed CD25-positive CTCL.
- Identify the optimal dose and schedule of pralatrexate for the treatment of relapsed or refractory CTCL.

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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 of Denileukin Diftitox and Pralatrexate in Relapsed/ Refractory Cutaneous T-Cell Lymphoma (CTCL)

Presentations discussed in this issue

Duvic M et al. **Efficacy of denileukin diftitox retreatment in patients with cutaneous T-cell lymphoma who relapsed after initial response.** *Proc ASH* 2010;**Abstract 2863**.

Horwitz SM et al. **Identification of an active well tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL): Final results of a multicenter dose finding study.** *Proc ASH* 2010;**Abstract 2800**.

Slides from presentations at ASH 2010 and transcribed comments from recent interviews with Steven M Horwitz, MD (12/29/10) and Francine Foss, MD (1/13/11)

Efficacy of Denileukin Diftitox Retreatment in Patients with Cutaneous T-Cell Lymphoma Who Relapsed After Initial Response[1]

Identification of an Active, Well-Tolerated Dose of Pralatrexate in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma (CTCL): Final Results of a Multicenter Dose-Finding Study (slide 8)[2]

[1]Duvic M et al.
Proc ASH 2010;Abstract 2863.

[2]Horwitz SM et al.
Proc ASH 2010;Abstract 2800.

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Efficacy of Denileukin Diftitox Retreatment in Patients with Cutaneous T-Cell Lymphoma Who Relapsed After Initial Response

Duvic M et al.

Proc ASH 2010;Abstract 2863.

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Study 93-04-14 Methods and Objectives

- Study 93-04-14 was a Phase III, multicenter, open-label study that evaluated the efficacy and safety of denileukin diftitox (DD) administered to patients with cutaneous T-cell lymphoma (CTCL) who had participated in three earlier trials of DD.
  - Patients from Study 93-04-11 randomly assigned to placebo, stable or progressive disease after 8 courses
  - Patients from Study 93-04-11 randomly assigned to DD, stable disease after 8 courses
  - **Patients from Studies 92-04-01, 93-04-10 and 93-04-11 who had relapsed after an initial response to DD**
  - Patients excluded from 93-04-11 due to being CD25 assay-negative
- The current analysis is limited to the DD relapsed and retreated cohort
- **Primary objective**: Overall response rate (ORR)
- **Secondary objectives**: Progression-free survival (PFS), time to treatment failure (TTF) and safety

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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Study 93-04-14 Design: Relapsed-Retreated Subgroup

Eligibility for Relapsed-Retreated Subgroup (N = 20)
Initial response to DD during Studies 92-04-01, 93-04-10 and 93-04-11 followed by relapse
Histopathologically confirmed Stage IA-III CTCL
≤3 prior treatment regimens
CD25 assay-positive expression

→ DD, IV 18μg/kg/d on days 1-5, q3wks up to 8 courses

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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Best Tumor Response Among Relapsed-Retreated Patients

Response	All Patients (n = 20)	Disease Stage at Baseline	
		Stage ≤IIA (n = 16)	Stage ≥IIB (n = 4)
ORR	40%	37.5%	50%
CR/CCR	10%	12.5%	0%
PR	30%	25%	50%
ORR, exact 95% CI	19.1, 63.9	15.2, 64.6	6.8, 93.2
SD	25%	18.8%	50%
PD	35%	43.8%	0%

CR = complete response; CCR = clinical complete response; PR = partial response; SD = stable disease; PD = progressive disease

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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Results Summary
Secondary Endpoints

- **PFS**
  - Median PFS = 205 days (Kaplan-Meier estimate)
  - Progression events were observed in 9/20 patients (45%), all of whom had Stage ≤IIA disease at baseline
- **TTF**
  - Median TTF = 189 days (Kaplan-Meier estimate)
  - Failure events were observed for 12/20 patients (60%)
- **Safety**
  - All 20 patients (100%) experienced ≥1 adverse event (AE) during treatment.
    - One patient (5%) had a treatment-related serious AE (pleural effusion)
  - The most common treatment-related AEs were nausea (35%), fatigue (25%), rigors (20%), headache (15%) and pyrexia (10%).
  - There were no instances of severe capillary leak syndrome or death.

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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Author Conclusions

- This is the first trial of DD therapy that included patients with relapsed CTCL who were retreated with DD.
- Patients with CD25-positive CTCL who responded and then relapsed during prior DD treatment can attain durable responses after DD retreatment.
- The ORR of 40% is similar to that seen during primary DD treatment, with an estimated median duration of response of 9.8 months (data not shown).
- The ORR of 40% and comparable duration of response suggest that any presence of anti-DD neutralizing antibodies generated during prior DD exposure does not affect retreatment with DD.
- Adverse events were generally mild to moderate in severity and reversible.
- The results of this study establish that DD retreatment is safe and effective in patients with relapsed CD25-positive CTCL.

Duvic M et al. *Proc ASH* 2010;Abstract 2863.

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Identification of an Active, Well-Tolerated Dose of Pralatrexate in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma (CTCL): Final Results of a Multicenter Dose-Finding Study

Horwitz SM et al.

Proc ASH 2010;Abstract 2800.

PDX-010 Study Objectives

- To determine an effective and well tolerated dose and schedule of pralatrexate for patients with relapsed or refractory CTCL (Stage 1 objective).
- To characterize the safety profile of pralatrexate in CTCL when administered with vitamin B_{12} and folic acid.
- To evaluate safety and efficacy for additional patients at the optimal dose (Stage 2 objective).
- **Eligibility**
  - Confirmed relapsed/refractory CTCL
  - Progression or relapse after ≥ 1 systemic therapy

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Objective Response Rates and Dose Limiting Toxicities (DLTs) in Stage 1

Cohort	Pralatrexate Dose (mg/m^2/week); Schedule	n	Patients with DLTs	Overall Response Rates (ORR)
1	30; 3/4 weeks	2	2	100%
2	20; 3/4 weeks	3	2	67%
3	20; 2/3 weeks	7	3	57%
4	15; 3/4 weeks	6	3	50%
5	15; 2/3 weeks	3	2	0%
6	10; 3/4 weeks	10	3	10%

Optimal dose and schedule selected as 15 mg/m^2 administered 3 out of 4 weeks (Cohort 4)

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

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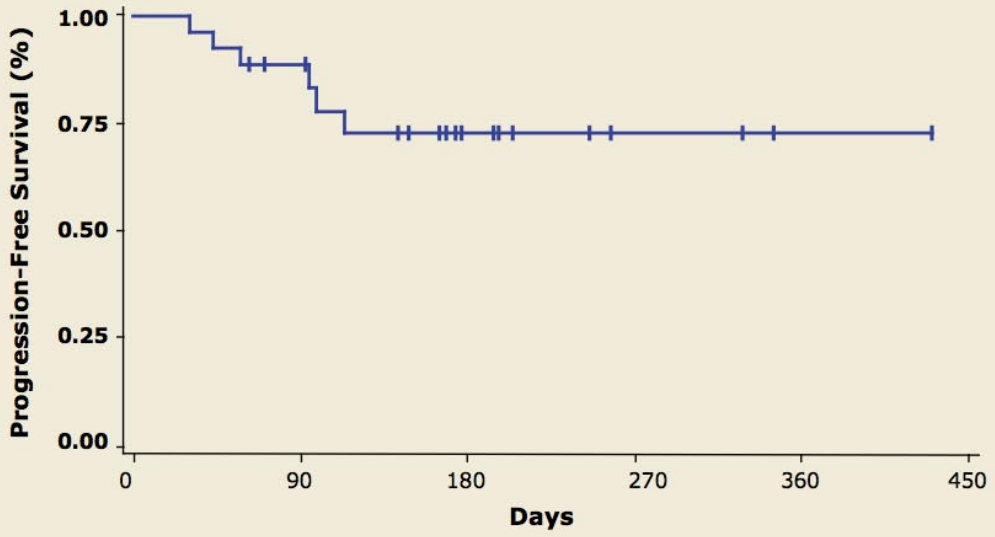
Progression-Free Survival at Optimal Dose and Schedule: Stage 2



With permission from Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

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Response Rates

	n	Response Rates
Patients on Optimal Dose and Schedule	29	45%
Patients on ≥ Optimal Dose and Schedule	41	51%
Patients on < Optimal Dose and Schedule	13	8%
All Patients	54	41%

Optimal Dose/Schedule: 15 mg/m² administered 3 out of 4 weeks

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

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Treatment-Related Adverse Events at Optimal Dose/Schedule

Adverse Events (AEs)	All Grades	Grade 3/4
Mucosal inflammation	48%	17%
Fatigue	38%	3%
Nausea	31%	0%
Vomiting	14%	0%
Anorexia	10%	0%
Thrombocytopenia	7%	3%

Optimal Dose/Schedule: 15 mg/m² administered 3 out of 4 weeks

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

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Author Conclusions

- Pralatrexate demonstrated high activity in patients with heavily pretreated relapsed/refractory CTCL.
  - ORR (at optimal dose and schedule) = 45%
  - PFS (at optimal dose and schedule) = Not reached
- Toxicity generally acceptable at the optimal dose/schedule.
  - Mucosal inflammation = 48% (primarily Grade 1/2)
  - Absence of Grade 3/4 neutropenia
  - Single event of Grade 3 thrombocytopenia
- Pralatrexate should be evaluated in earlier lines of therapy and also in combination with other therapeutics in CTCL.

Horwitz SM et al. *Proc ASH* 2010;Abstract 2800.

Investigator comments on pralatrexate and denileukin diftitox (DD) in relapsed or refractory CTCL

Our study investigated pralatrexate in a dose de-escalation design in CTCL. As long as there was some activity, we would dose reduce to the next lower level. In the first part of the study, we identified two active doses with reasonable toxicity: 15 mg/m^2 three out four weeks and 20 mg/m^2 two out of three weeks.

Because the toxicities were a little less clinically significant in the 15 mg/m^2 cohort, that was expanded in part 2. Almost no hematologic toxicity was observed with some Grade 2 or 3 mucositis in the expanded cohort. The median duration of response was not reached at the time of the presentation. Pralatrexate, at an easier dose and schedule, appears quite active in CTCL for long-term use.

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

The first trials of DD didn't use steroid premedication. Consequently, a number of patients developed infusion reactions. Now when we use DD in practice, we administer steroid premedication. The incidence of infusion-related reactions has gone down significantly. We manage vascular leak with diuresis and IV fluids, if needed.

Interview with Francine Foss, MD, January 13, 2011