5 Minute JournalClub

Key ASH Presentations
Issue 6, 2012

Chemotherapy and Rituximab for NHL: Results from the Dose-Adjusted EPOCH Study

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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 and new information 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, 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

- Consider the inclusion of single-agent romidepsin in the treatment algorithm for relapsed or refractory peripheral T-cell lymphoma.
- Integrate new and existing therapeutic strategies into the best-practice management of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with relapsed/refractory mantle-cell lymphoma.
- Recall new data with investigational agents demonstrating promising activity in non-Hodgkin lymphomas.

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To go directly to slides and commentary for this issue, **click here**.

This past Friday 8 clinical investigators ventured to Miami for our annual post-ASH lymphoma Think Tank. Over the course of more than 6 fascinating hours together we focused on a multitude of topics and as always recorded the proceedings, which will be available as an enduring activity in the coming months. While our engineers are busy de-umming (our little secret) and editing the audio, we thought we would hold you over with a taste of some of the new ASH NHL papers that were fodder for discussion and debate during Friday's lymphoma extravaganza.

1. Lenalidomide/rituximab

The so-called R-squared regimen of the immunomodulatory agent lenalidomide (len) and rituximab (R) has generated considerable excitement among investigators, and at ASH we saw the results from a Phase II trial evaluating this combination alone or with dexamethasone for patients with relapsed indolent NHL or mantle-cell lymphoma (MCL) considered to be resistant to R. Of the 48 patients treated on the trial more than a third had a response, and the median progression-free survival was 18 months. These findings have raised hopes that len might help overcome R resistance and that in select populations such as the elderly this combination might become an alternative to aggressive treatment of relapsed disease — for example, with autologous stem cell transplant (ASCT).

2. Two papers on MCL

Another ASH NHL highlight was the presentation of a Phase II study of PCI-32765, an oral irreversible Bruton's tyrosine kinase inhibitor, as a single agent in relapsed/refractory MCL. The results are compelling, as two thirds of the 39 patients in the study had objective responses and 35 remain on treatment. Importantly, none stopped therapy due to toxicity. Many investigators now have patients in their practices on trials who have experienced obvious prolonged benefit with this agent, and as a result significant excitement surrounds it and other small molecules, like the PI3 kinase inhibitor CAL-101 that is also under active investigation in a variety of NHL subtypes.

The rarity of MCL has made the definition of treatment benefits a challenge, and another important study reported at ASH attempted to better establish the effects of R in this disease. This effort from the UK evaluated the combination of fludarabine and cyclophosphamide with or without R, and while a high rate of infection was observed in these patients receiving fludarabine, substantial improvements in response rate and an almost doubling of progression-free survival reinforced the value of adding the CD20 antibody, which is now used routinely up front and often as maintenance treatment.

3. Two studies of diffuse large B-cell lymphoma (DLBCL)

Previous research with dose-adjusted EPOCH with R has shown promising results in untreated DLBCL, and this **Phase IV trial** of 81 patients with poor-prognosis disease (age-adjusted IPI of 1 or higher) reported an encouraging 62% 5-year progression-free survival rate. An ongoing Phase III Intergroup trial is comparing EPOCH-R to R-CHOP.

One of the biggest disappointments at ASH came from the much-awaited **Phase III SWOG study** comparing conditioning R/BEAM (carmustine, etoposide, cytarabine, melphalan) to ^{131}I-tositumomab/BEAM for patients with DLBCL about to undergo ASCT. The trial results were flat-out negative, confounding the positive findings observed in the Phase II setting and forcing investigators back to the drawing board to look at higher doses of radioimmunotherapy as pretransplant conditioning.

4. Two papers on T-cell lymphoma

At ASH Dr Bertrand Coiffier presented an update of the Phase II pivotal study evaluating the selective inhibitor of histone deacetylase romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL). This trial, which led to the FDA approval in this setting, evaluated 130 patients across PTCL subgroups, and these findings reveal higher response rates among individuals with the most common forms of the disease. This suggests that romidepsin may perhaps have more activity in common PTCL subtypes than initial data suggested.

In cutaneous T-cell lymphoma we saw the results of a Phase II trial investigating the interesting sequence of pegylated liposomal doxorubicin (PLD) — which has been shown to have high response rates and is known to concentrate in the skin — followed by the synthetic retinoid bexarotene (Bex). Perhaps because the study selected for patients with more aggressive disease, a 41% response rate (lower than reported in other trials) was observed with PLD and Bex did not increase the rate or duration of response. With the current shortage of PLD, not many patients are being treated with this agent.

Next up on this ASH series we go back to multiple myeloma and new reports on effective long-term disease control in older patients on continuing therapy.

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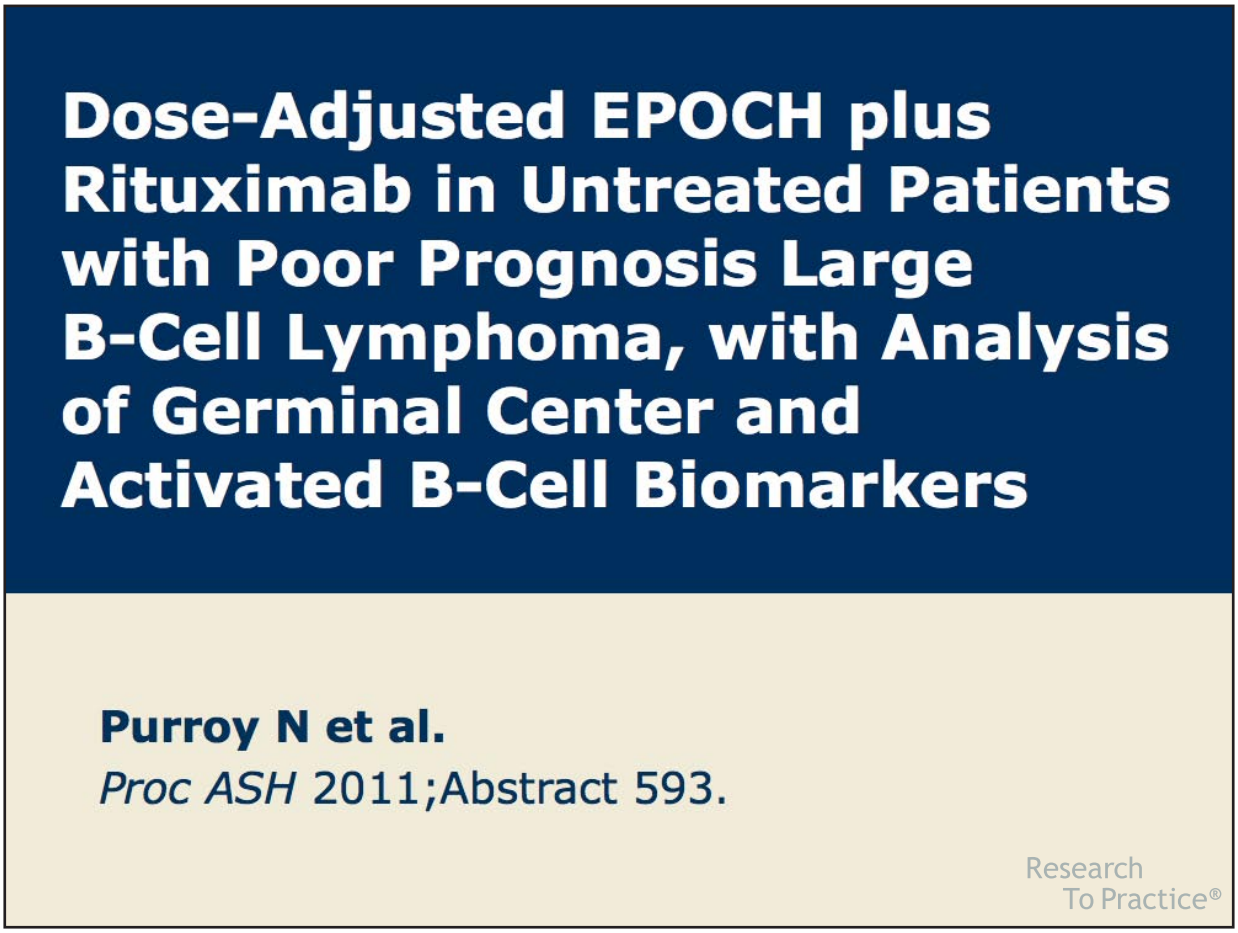
Chemotherapy and Rituximab for NHL: Results from the Dose-Adjusted EPOCH Study

Presentation discussed in this issue

Purroy N et al. **Dose-adjusted EPOCH plus rituximab in untreated patients with poor prognosis large B-cell, with analysis of germinal center and activated B-cell biomarkers. A Phase IV study conducted by the Spanish PETHEMA group.** *Proc ASH* 2011;**Abstract 593**.

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Owen A O'Connor, MD, PhD (2/3/12) and Craig Moskowitz, MD (1/11/12)



Background

- Patients with large B-cell lymphomas treated with front-line, dose-adjusted EPOCH (DA-EPOCH) have a complete response (CR) rate of 92% and 5-year progression-free survival (PFS) of 70% (*Blood* 2002;99:2685).
- Combination of rituximab (R) with DA-EPOCH (DA-EPOCH-R) showed promising results in patients with untreated diffuse large B-cell lymphomas (DLBCL) (*J Clin Oncol* 2008;26:2717; *Br J Haematol* 2007;136:276).
- **Current study objective**: Assess the efficacy and safety of DA-EPOCH-R in patients with untreated large B-cell lymphomas with poor prognosis in a Phase IV study.

Purroy N et al. *Proc ASH* 2011;Abstract 593.

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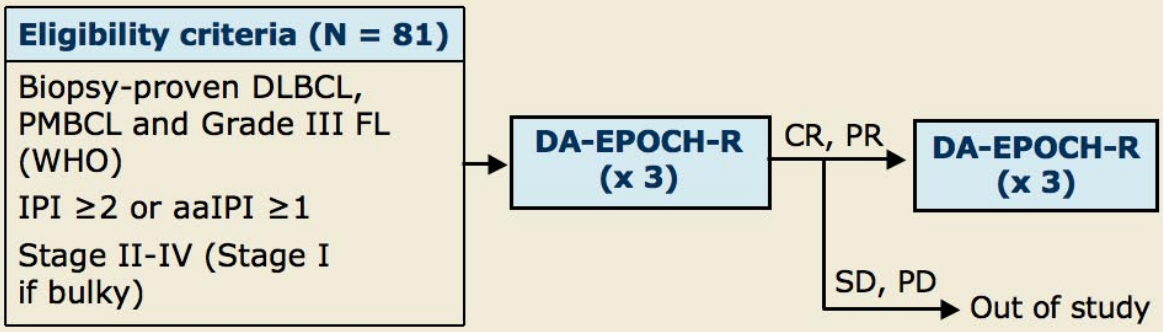
Phase IV Study Design



- Tumor samples analyzed by IHC for biomarkers of proliferation (Ki-67) and markers of cellular differentiation.
- IHC to determine the histological origin of patients according to the Choi and Hans algorithms was performed retrospectively.
- Follow-up: Evaluation every 3 mo for 2 y, then every 6 mo for 3 y

Primary endpoint: PFS

Purroy N et al. *Proc ASH* 2011;Abstract 593.

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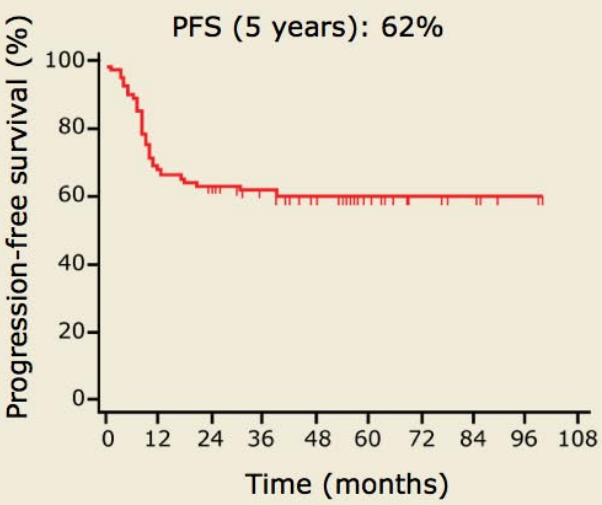
DA-EPOCH-R Dosing Schedule

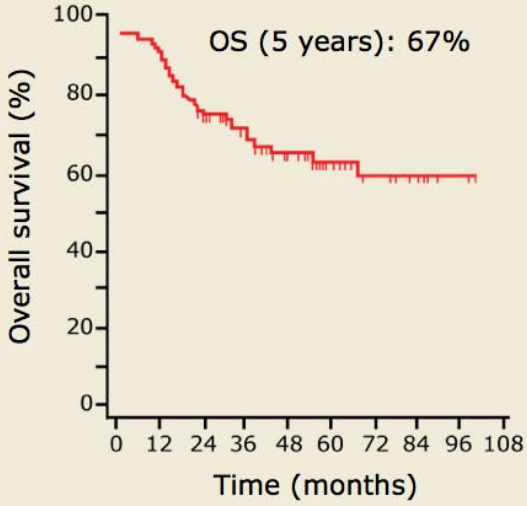
Drug	Dose	Treatment days
Etoposide (CIV)	50 mg/m^2/day	1,2,3,4
Doxorubicin (CIV)	10 mg/m^2/day	1,2,3,4
Vincristine (CIV)	0.4 mg/m^2/day	1,2,3,4
Rituximab (IV)	375 mg/m^2/day	1
Cyclophosphamide (IV)	750 mg/m^2/day	5
Prednisone (PO)	60 mg/m^2/day	1,2,3,4,5

- Radiation therapy (30 Gy): For bulky/residual disease
- Cycles administered q3wk if ANC ≥1 x 10^9/L and platelet ≥100 x 10^9/L
- After every cycle, doses were adjusted according to known hematological parameters
- For neutropenic fever, dose reduced 20% below the last cycle

Purroy N et al. *Proc ASH* 2011;Abstract 593.

PFS and OS





Median follow-up: 55 months

With permission from Purroy N et al. *Proc ASH* 2011;Abstract 593.

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Complete Response Rates in Patient Subgroups

Characteristic	CR rate	*p*-value
IPI 0-2 (n = 13) 3-5 (n = 68)	 100% 75%	0.06
Choi algorithm GCB (n = 22) ABC (n = 17)	 86.3% 88.2%	1.0
Hans algorithm GCB (n = 16) Non-GCB (n = 23)	 81.2% 91.3%	0.631
Ki-67 <80% (n = 29) ≥80% (n = 29)	 82.7% 86.7%	1.0

GCB = germinal center B cell; ABC = activated B cell

Overall (N = 81) CR/uCR: 80.2%, PR: 9.9%, failure rate: 9.9%

Purroy N et al. *Proc ASH* 2011;Abstract 593.

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Adverse Events

Adverse event (N = 81)	Incidence (%)
Anemia (Grade 3/4)	84.0%
Thrombocytopenia (Grade 3/4)	71.6%
Neutropenic fever	45.7%
Mucositis (Grade 3/4)	11.1%
Neurotoxicity (Grade 3/4)	2.5%

Discontinuation: 6 patients, 2 due to disease progression

Deaths: 4 (pneumonia: 2, septic shock: 2)

Purroy N et al. *Proc ASH* 2011;Abstract 593.

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Author Conclusions

- Patients with DLBCL who had adverse prognostic features showed a high response rate to DA-EPOCH-R.
- PFS was 62% at 5 years and was comparable to dose-dense or other high-dose regimens.
- DA-EPOCH-R seems to diminish the impact of adverse clinical variables and the value of histological origin and tumor proliferation (data not shown).
- Randomized studies comparing R-CHOP to DA-EPOCH-R in patients with high-risk DLBCL are warranted.

Purroy N et al. *Proc ASH* 2011;Abstract 593.

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Investigator Commentary: Dose-Adjusted EPOCH with Rituximab in Patients with Untreated Poor-Prognosis Large B-Cell Lymphoma

This is an interesting, large, single-arm study evaluating dose-adjusted EPOCH in a patient population with an age-adjusted IPI of 1 or higher. They reported an overall response rate of about 90%, with 80% of patients having a CR and an overall survival of 67%. In the absence of a randomized trial it is hard to determine whether this regimen is better than R-CHOP-21. When the Intergroup study comparing R-CHOP to EPOCH-R is completed, we should have good evidence indicating whether we can improve on the standard R-CHOP regimen.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

In comparison to these data, the study by Pfreundschuh and colleagues (*Proc ASH* 2011;Abstract 592) showed better efficacy. Because the dose of EPOCH-R is adjusted based on blood counts, it requires a costly double-lumen catheter procedure in which patients are admitted for 5 days every 3 weeks. Hence, for the EPOCH-R regimen to be used, especially in the United States, it will have to be superior to R-CHOP-21 in an Intergroup study.

Interview with Craig Moskowitz, MD, January 11, 2012