5 Minute JournalClub

Key ASH Presentations
Issue 9, 2012

Prognostic Impact of FDG-PET in FL

For more visit ResearchToPractice.com/5MJCASH2012

Research To Practice®

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

- Develop evidence-based treatment algorithms for patients presenting with high tumor mass follicular lymphoma (FL).
- Optimize outcomes for patients with relapsed or refractory FL through the application of emerging clinical research data.
- Evaluate the benefits and risks of therapy with different monoclonal antibodies as mono- or combination therapy in the treatment of relapsed or refractory FL or other indolent non-Hodgkin lymphomas or previously untreated chronic lymphocytic leukemia.
- Compare and contrast the benefits and risks of radioimmunotherapy and standard immunochemotherapy in the management of newly diagnosed FL.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2012/9/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Jonathan W Friedberg, MD, MMSc
Professor of Medicine and Oncology
Chief, Hematology/Oncology Division
James P Wilmot Cancer Center
University of Rochester
Rochester, New York

Advisory Committee: Cephalon Inc, Genentech BioOncology; Consulting Agreement: Mundipharma International Limited; Data and Safety Monitoring Board: Lilly USA LLC; Paid Research: Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

Stephanie A Gregory, MD
The Elodia Kehm Chair of Hematology
Professor of Medicine
Director, Section of Hematology
Rush University Medical Center
Chicago, Illinois

Paid Research: Celgene Corporation, MedImmune Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc; Scientific Advisory Board: Amgen Inc, Genentech BioOncology, Spectrum Pharmaceuticals Inc, Teva.

Brad S Kahl, MD
Associate Professor
Director, Lymphoma Service
University of Wisconsin School of Medicine and Public Health
Associate Director for Clinical Research
UW Carbone Cancer Center
Madison, Wisconsin

Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology, GlaxoSmithKline, Millennium: The Takeda Oncology Company.

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine, Weill Cornell Medical College
New York, New York

Consulting Agreements: Celgene Corporation, Cephalon Inc, Genentech BioOncology, GlaxoSmithKline, Millennium: The Takeda Oncology Company.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abbott Laboratories, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/ Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Last review date: April 2012
Expiration date: April 2013

5 MinuteJournalClub

Key ASH Presentations
Issue 9, 2012

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

For this concluding post-ASH summary we focus on a smattering of data sets that shed additional light on a number of relevant clinical questions and therapeutic strategies in the management of indolent NHL, including follicular lymphoma (FL) and CLL:

1. Rituximab (R)/lenalidomide (len) in CLL

Previous preclinical work suggested that the effect of len on natural killer cell expansion enhanced the cytotoxic impact of R, and on that basis several trials evaluating the "R squared" combination were launched, including 3 studies reported at ASH. The first was a Phase II effort evaluating R/len in 59 patients with relapsed/refractory CLL, and the combination produced an impressive overall response rate of 66% with a median time to treatment failure of 24 months. A second Phase II study attempted to assess the combination in patients with previously untreated disease, and more than 75% of patients responded. Finally, an encouraging Phase I-II study evaluating fludarabine/R and escalating doses of len as induction therapy followed by R/len maintenance in 45 previously untreated patients resulted in a 49% CR rate, but dose-limiting toxicity (mainly dermatologic) was observed in more than a third of participants. Len is currently only used by most investigators in very advanced refractory CLL.

2. Alemtuzumab/fludarabine/cyclophosphamide (AFC) in patients with high-risk CLL requiring treatment

At ASH, our understanding of how to integrate alemtuzumab into the treatment algorithm for CLL once again hit a bump in the road with the report from a Phase III trial evaluating low-dose subcutaneous A in combination with FC versus FC alone. Although the addition of the anti-CD52 antibody resulted in slightly better cancer outcomes, substantial toxicity was observed, including flulike symptoms and infection related to immune suppression, and as such this approach remains investigational.

3. Obinutuzumab (GA101)

ASH provided a vivid reminder of the impressive activity of anti-CD20 antibody treatment in B-cell lymphomas with the first results of the landmark ECOG RESORT trial commented on earlier in this series, in which the control arm of 4 weekly doses of R resulted in a 70% response rate, and without further treatment, 86% of patients who responded were progression free at 3 years.

The activity of this bellwether biologic agent is the reason there was great interest in 3 ASH data sets evaluating obinutuzumab (O) — a novel glycoengineered type 2 anti-CD20 MAB with a different functional profile than rituximab (more direct cytotoxicity and cell death but slightly less complement-dependent cytotoxicity). The first, a Phase I-II trial, reported objective responses in patients considered resistant to R, while the second, a randomized Phase II study with 175 patients comparing O to R as single agents in the relapsed setting, showed response rates modestly favoring O. Finally, a Phase I study looked at the agent in combination with CHOP or FC and provided confidence that a large Phase III trial comparing R-CHOP to O-CHOP is feasible.

4. Two data sets on up-front radioimmunotherapy (RIT) in FL

A much anticipated and somewhat disappointing SWOG trial of R-CHOP versus CHOP followed by ^{131}I-tositumomab consolidation demonstrated similar efficacy and tolerability with a few more cases of AML/MDS in the RIT arm (7 versus 3). The study raises natural questions about a more comprehensive strategy of R/chemo followed by RIT consolidation and R maintenance, which is the approach used in a subsequent Phase II SWOG study that has completed accrual but has not yet reported. Another ASH Phase II report focused on RIT alone up front — this time with 2 fractions of ^{90}Y ibritumomab. Thirteen of 76 patients received pretreatment with R in an attempt to clear bone marrow involvement greater than 20%, and 11 of the 13 were able to receive RIT. A median PFS of 36 months was observed, with manageable hematologic toxicity. However, RIT monotherapy up front is rarely utilized in clinical practice pending more definitive trial data.

5. [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scans in FL

At ASH we saw the results of a study of interim and end-of-treatment FDG-PET scans in 121 patients with FL receiving R-CHOP. Approximately one quarter had positive end-of-treatment scans, and not surprisingly 2-year PFS and OS were worse in this group. (About half of all patients with positive scans at the end of treatment had disease progression at 2 years.) The challenge of managing these patients remains unanswered and, hopefully, more guidance will come from future clinical research.

6. Bortezomib in FL

A prior report from the 676-patient randomized Phase III LYM3001 study of R alone or with bortezomib in relapsed/refractory disease demonstrated a modest advantage to the combination, and at ASH an impressive translational data set was presented looking at prespecified sera and tissue endpoints that identified a subset of approximately a third of patients in the trial who achieved a greater benefit with the addition of bortezomib. These markers are not "ready for prime time" but are sure to be looked at in studies like ECOG-E2408, evaluating bendamustine/rituximab (BR) followed by R versus bortezomib/BR followed by R versus BR followed by R/len in high-risk FL.

Next we return to our recent breast cancer Patterns of Care survey, this time focusing on management of HER2-positive tumors in the early and advanced disease setting.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

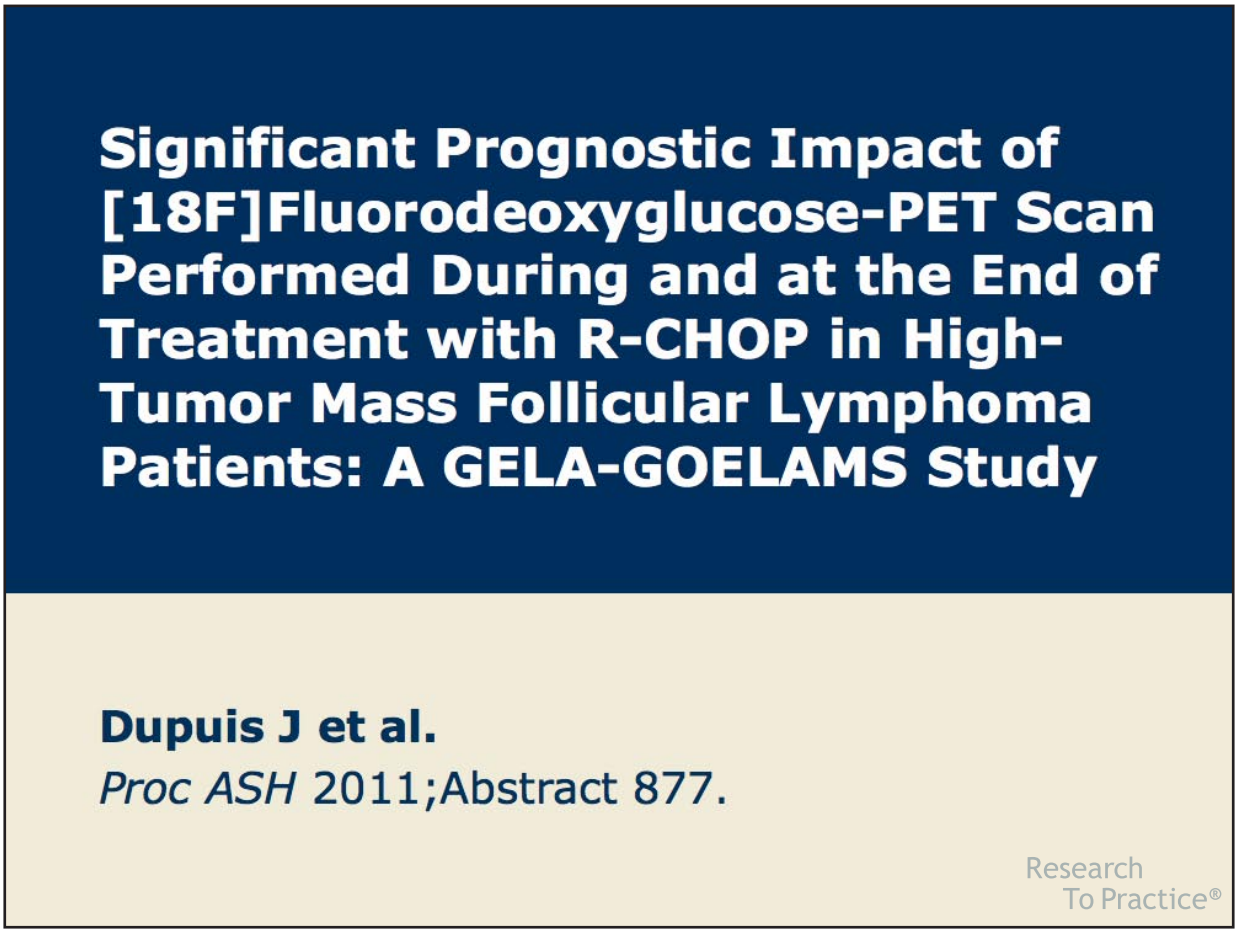
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Prognostic Impact of FDG-PET in FL

Presentation discussed in this issue

Dupuis J et al. **Significant prognostic impact of [18F]fluorodeoxyglucose-PET scan performed during and at the end of treatment with R-CHOP in high-tumor mass follicular lymphoma patients: A GELA-GOELAMS study.** *Proc ASH* 2011;**Abstract 877**.

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Stephanie A Gregory, MD (1/11/12) and Brad S Kahl, MD (1/26/12)



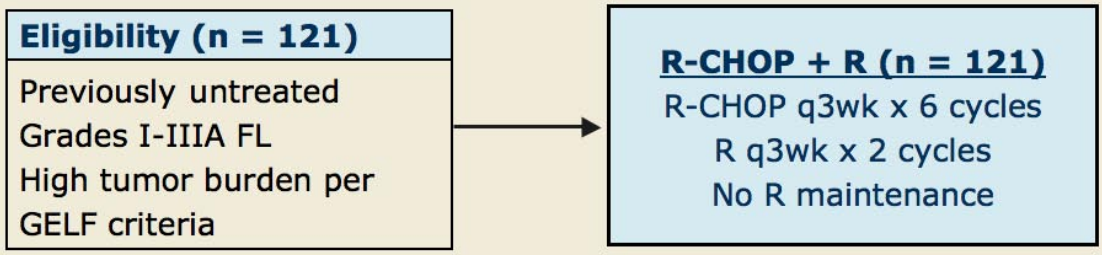
Background

- Patients with follicular lymphoma (FL) usually respond well to initial treatment with immunochemotherapy, which also increases survival benefits.
- However, a small proportion of patients relapse or develop refractory disease.
- The identification of this subgroup of patients can lead to early therapeutic interventions, potentially leading to better prognosis.
- Little is known about the use of [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with FL, although it is widely used for the staging and restaging of aggressive lymphomas.
- **Objective:**
  - Evaluate the prognostic value of FDG-PET performed in the middle and at the end of treatment in patients with high tumor mass FL treated with first-line immunochemotherapy.

Dupuis J et al. *Proc ASH* 2011;Abstract 877.

Research To Practice®

GELA-GOELAMS Trial Design



R-CHOP = rituximab (R), cyclophosphamide, doxorubicin, vincristine, prednisone

- FDG-PET was performed
  - Before treatment (initial FDG-PET)
  - After 4 cycles of R-CHOP (interim FDG-PET)
  - At the end of treatment (final FDG-PET)
- FDG-PET scans were first interpreted in each center, then centrally reviewed by 3 investigators blinded to clinical data.
- Positivity or negativity was rated according to the Deauville visual semi-quantitative criteria.

Dupuis J et al. *Proc ASH* 2011;Abstract 877.

Research To Practice®

Centrally Reviewed* FDG-PET Scans (Abstract)

Time of FDG-PET scan	Positive scans	Negative scans
Initial FDG-PET (n = 118)	99%	1%
Interim (I)-FDG-PET (n = 111)	24%	76%
Final (F)-FDG-PET (n = 106)	22%	78%

* The Kappa coefficient indicated a good degree of concordance among the 3 PET reviewers.

- Positivity was defined as fixation at level 4 (FDG uptake superior to that of the liver) or 5 (FDG uptake clearly superior to liver and/or new sites of disease).

Dupuis J et al. *Proc ASH* 2011;Abstract 877.

Research To Practice®

Survival Rates (Abstract)

Response	I-PET-negative	I-PET-positive	*p*-value
2-y PFS	86%	61%	0.0046
Response	**F-PET-negative**	**F-PET-positive**	***p*-value**
2-y PFS	87%	51%	<0.0001
2-y OS	100%	88%	0.0128

PFS = progression-free survival; OS = overall survival

Dupuis J et al. *Proc ASH* 2011;Abstract 877.

Research To Practice®

Author Conclusions

- In patients receiving first-line therapy for FL, FDG-PET scans performed either after 4 cycles of R-CHOP or at the end of immunochemotherapy induction are strongly predictive of treatment outcomes.
- Therapeutic intervention based on PET results during inductive treatment should be evaluated in the future.

Dupuis J et al. *Proc ASH* 2011;Abstract 877.

Research To Practice®

Investigator Commentary: Significant Prognostic Impact of [18F]Fluorodeoxyglucose-PET Scans — A GELA-GOELAMS Study

The evaluation of PET scans is a recommended criterion at the end of treatment for diffuse large B-cell lymphoma. Importantly, a negative PET scan is needed for long-term survival and cure. PET scanning has never been a recommendation for low-grade lymphomas because results reveal some as positive PET scans and others as negative scans. Because FLs have a high avidity for PET scanning, they are often positive on initial evaluation. This study demonstrated that negative PET scans are significant, as a longer PFS was observed in these cases. As such, it may be helpful to perform PET scanning at the end of treatment in low-grade lymphomas, especially in patients with bulky masses.

Interview with Stephanie A Gregory, MD, January 11, 2012

This is an interesting study demonstrating that PET scans at the end of treatment are good predictors of treatment outcome as indicated by the 2-year PFS rates. A modest OS difference was also seen based on the final PET scans. Although this trial does not give information about what to do with the patients with F-PET-positive scans, these data indicate that about 50% of these patients will relapse and 12% will die.

Interview with Brad S Kahl, MD, January 26, 2012