5 Minute JournalClub

Key ASH Presentations
Issue 6, 2011

R-CHOP-21 Followed by I-131 Tositumomab Consolidation in Diffuse Large B-Cell Lymphoma (DLBCL)

For more visit ResearchToPractice.com/5MJCASH2011

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 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 OBJECTIVE

- Recall survival and toxicity results with R-CHOP followed by iodine-131 tositumomab consolidation as initial management of DLBCL.

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 educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim 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 presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

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:

Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Member, Lymphoma Service
Memorial Sloan-Kettering Cancer Center
New York, New York

Advisory Committee: Cephalon Inc, Genentech BioOncology, Seattle Genetics; Paid Research: Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

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: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals 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, Lilly USA LLC, Millennium — The Takeda Oncology Company, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

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 program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Last review date: March 2011
Expiration date: March 2012

5 MinuteJournalClub

Key ASH Presentations
Issue 6, 2011

Click here for ASH papers on MCL and DLBCL.

Imagine you were given the opportunity to have one of the great figures in hematologic oncology visit your practice for a day, meet patients in your clinic and review their cases. Medical oncologist Dr Margaret Deutsch of Raleigh, North Carolina accepted that challenge and some months ago welcomed lymphoma maven and rock guitarist Bruce Cheson to the Tar Heel State as part of our ***Visiting Professors series.*** The very first patient they met together typified a modern dilemma faced by both community practitioners and investigators. This otherwise-healthy 62-year-old woman presented with a benign-appearing submandibular lymph node that was initially treated with antibiotics but proved to be mantle-cell lymphoma (MCL). Further workup revealed extensive adenopathy in the neck and mediastinum.

It's disappointing that more than a decade after identifying the biologic alteration that differentiates mantle-cell from the other lymphomas — t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1 — we still have not found an imatinib/CML-like solution for this generally incurable disease. Dr Cheson — who seems to have

Dr Cheson and the Oncotones perform at the House of Blues, 10 PM Sunday, during the 2010 ASCO Meeting.

published a paper on every possible NHL subtype and issue — echoed this reality as he immediately raised the possibility of participation in a clinical trial when discussing Dr Deutsch's patient following their meeting. He then rattled off a host of promising biologic agents, including the much-discussed PI3 kinase inhibitor CAL-101 and others I had never heard of, like Bruton tyrosine kinase (BTK) inhibitors and BiTEs (bispecific T-cell engagers).

Bruce also mentioned two important Phase III trials for newly diagnosed MCL: the planned Intergroup trial of pretransplant induction with either R-hyper-CVAD or BR (bendamustine/rituximab) and in the nontransplant setting — stealing a page from myeloma — a proposed study featuring an initial randomization of BR versus BR/bortezomib with a second randomization to maintenance with either R or R/lenalidomide.

Despite all this fascinating science and hope for the future, Dr Deutsch was still faced with a young woman with a bad disease and no great solutions for today. As is often my observation when community docs have investigators review their cases, Maggie almost seemed relieved to know that one of the leading minds in the field didn't really have much more to offer this unfortunate patient.

Below we review several ASH papers on mantle-cell and diffuse large B-cell lymphoma (DLBCL) that hopefully will help lead the way for the Oncotones to play happier tunes in the future.

1. **European MCL Network trial**: R-CHOP alternating with R-DHAP followed by high-dose Ara-C prior to transplant

This high-profile study provided provocative data demonstrating a progression-free survival advantage to inclusion of high-dose Ara-C, and the authors concluded that this "should become the new standard of care for MCL patients up to 65 years."

2. **Italian study** of lenalidomide/dexamethasone in relapsed/refractory MCL

In this Phase II trial of 33 patients the objective response rate to salvage therapy was 67 percent, which is similar to that with lenalidomide alone. Interestingly, an increase in bone marrow macrophage infiltration was observed, likely a result of the immunomodulatory effect of lenalidomide, resulting in increased microvessel counts and suggesting a unique mechanism of "indirect angiogenesis."

3. **SWOG Phase II trial** of consolidation with radioimmunotherapy (RIT) after R-CHOP induction for DLBCL

This disappointing study demonstrated that I-131 tositumomab did not seem to add much to outcome, although 27 percent of the patients never received RIT because of early relapse and induction treatment complications.

4. **Memorial trial in mediastinal large B-cell lymphoma**

This Phase II study of 54 patients with a median age of 33 employed an initial nonradiation therapy approach of dose-dense R-CHOP followed by ICE/RICE consolidation. Treatment failure occurred in 11 patients, but five are now progression

free after salvage autotransplant with radiation treatment. The authors believe that radiation therapy may now be avoided up front, potentially sparing these younger patients the long-term sequelae of that treatment.

Next up on this ASH highlights program: Part 2 of our myeloma update and the next generation of IMiDs® and proteasome inhibitors.

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 each educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in each activity.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

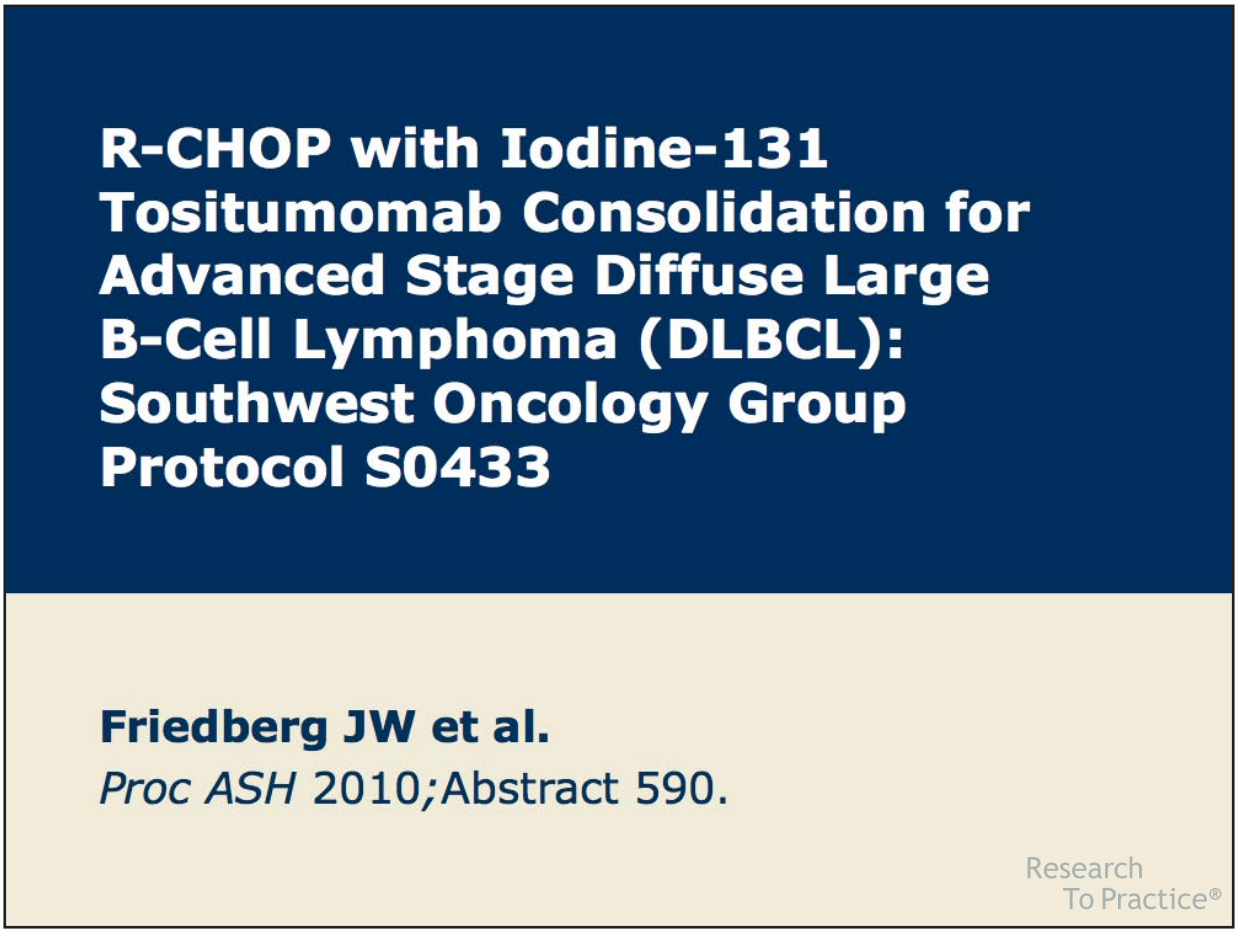
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

R-CHOP-21 Followed by I-131 Tositumomab Consolidation in Diffuse Large B-Cell Lymphoma (DLBCL)

Presentation discussed in this issue

Friedberg JW et al. **R-CHOP with iodine-131 tositumomab consolidation for advanced stage diffuse large B-cell lymphoma (DLBCL): Southwest Oncology Group protocol S0433.** *Proc ASH* 2010;**Abstract 590**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Craig Moskowitz, MD (1/3/11)



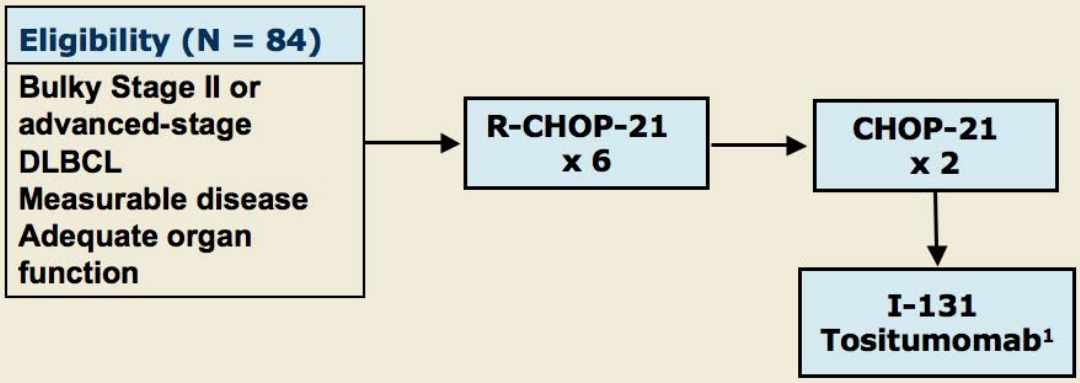
Background

- A substantial proportion of patients with advanced DLBCL and other clinical risk factors are not cured by R-CHOP chemotherapy.
- Therapeutic options with low toxicity are needed for the majority of DLBCL patients who are over age 60.
- Radioimmunotherapy (RIT) is a low toxicity treatment option that has been shown to
  - Have activity in relapsed DLBCL (*Blood* 2007;110:54)
  - Improve progression-free survival when used as consolidation therapy in advanced follicular lymphoma (*JCO* 2008;26:5156)

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

S0433: Phase II Trial of Consolidative RIT in DLBCL



[1] I-131 tositumomab 65 cGy was administered if platelet count between 100,000 and 150,000/mm^3 or 75 cGy if normal platelet count. I-131 tositumomab was administered 30 to 60 days after last dose of CHOP.

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

Patient Characteristics

Characteristic	N = 86
Median Age, Years (Range)	64 (29-85)
International Prognostic Index	
Low Risk	24%
Low-Intermediate Risk	32%
High-Intermediate Risk	32%
High Risk	12%

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

I-131 Tositumomab Administration

- Twenty-three patients (27%) did not receive I-131 tositumomab:
  - Early progression: 3 patients
  - Adverse event or death: 9 patients
  - Refusal: 6 patients
  - Other reasons: 5 patients
- Patients who did not receive I-131 tositumomab were more likely to have high-intermediate/high IPI-risk disease compared to those who received therapy.
  - 60% versus 35% (p = 0.004)

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

Efficacy Outcomes (Median Follow-Up 1.2 Years)

Outcome	N = 84
One-Year Overall Survival Estimate (95% CI)	85% (77-93%)
One-Year Progression-Free Survival Estimate (95% CI)	75% (65-85%)

Prior experience from population-based registry used to estimate survival rates for patient population of this study based on IPI score distribution:

- Estimated, adjusted one-year overall survival rate: 86%
- Estimated, adjusted one-year progression-free survival rate: 80%

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

Common Serious Adverse Events (N = 84)

Adverse Event	Grade 3	Grade 4
Hematologic	19%	54%
Infection	15%	1%
Flu-like symptoms	12%	1%
Neuropathy	11%	—

- Five treatment-related Grade 5 adverse events occurred:
  - Cardiac ischemia = 2
  - Acute myelogenous leukemia = 1
  - Renal failure = 1
  - Febrile neutropenia = 1

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

Author Conclusions

- A consolidation strategy utilizing iodine-131 tositumomab after 8 cycles of CHOP chemotherapy (6 with rituximab) for advanced-stage DLBCL does not appear to be promising.
  - Early progressions, deaths and declining performance status during CHOP chemotherapy limit the number of patients who ultimately can benefit from a planned consolidation approach
  - Relapse events occurred in the group who received consolidation despite more favorable prognostic features
- Incorporation of novel agents earlier in therapy may have more impact in DLBCL than consolidation or maintenance approaches.

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Research To Practice®

Investigator Comment on R-CHOP with Iodine-131 Tositumomab Consolidation for Advanced-Stage Diffuse Large B-Cell Lymphoma (DLBCL)

The results from this Phase II study from SWOG are in contrast to a study at Memorial Sloan-Kettering, where we administered R-CHOP followed by yttrium-90 ibritumomab and showed excellent results in a similar patient population.

The issue I see with this presentation is that the data are only analyzed for the intent-to-treat (ITT) population. A number of patients experienced disease progression prior to receiving radioimmunotherapy, and if the data were analyzed by therapy received — meaning in patients who received R-CHOP followed by I-131 tositumomab consolidation — I suspect the results would have appeared much better. We suggested this to the presenter, and I suspect they will review the data and analyze them based upon therapy received, in addition to the ITT population.

Interview with Craig Moskowitz, MD, January 3, 2011

Research To Practice®