5 Minute JournalClub

Key ASH Presentations
Issue 6, 2011

High-Dose Ara-C with R-CHOP and Autologous Stem Cell Transplant (ASCT) in Mantle-Cell Lymphoma

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

- Counsel younger patients with newly diagnosed mantle-cell lymphoma about the benefits and risks of aggressive induction therapy, including the contribution of high-dose Ara-C.

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:

Lauren C Pinter-Brown, MD
Director, UCLA Lymphoma Program
Clinical Professor of Medicine
Geffen School of Medicine at UCLA
Los Angeles, California

Advisory Committee: Allos Therapeutics, Celgene Corporation, Genentech BioOncology, Millennium — The Takeda Oncology Company; Consulting Agreement: Allos Therapeutics; Speakers Bureau: Genentech BioOncology.

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.

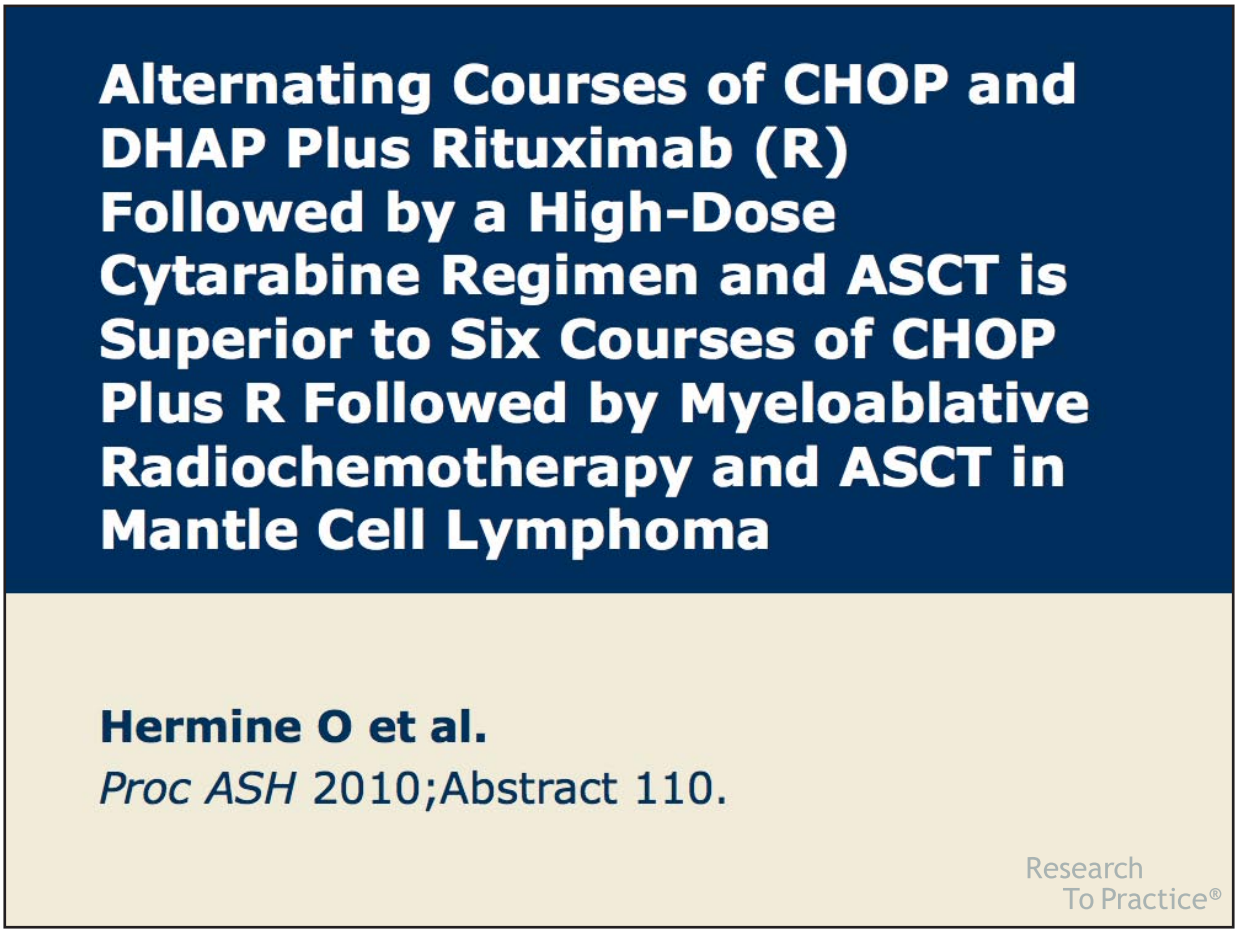
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

High-Dose Ara-C with R-CHOP and Autologous Stem Cell Transplant (ASCT) in Mantle-Cell Lymphoma

Presentation discussed in this issue

Hermine O et al. **Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high-dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger trial of the European Mantle Cell Lymphoma Network (MCL net).** *Proc ASH* 2010;**Abstract 110**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Lauren C Pinter-Brown, MD (1/7/11)



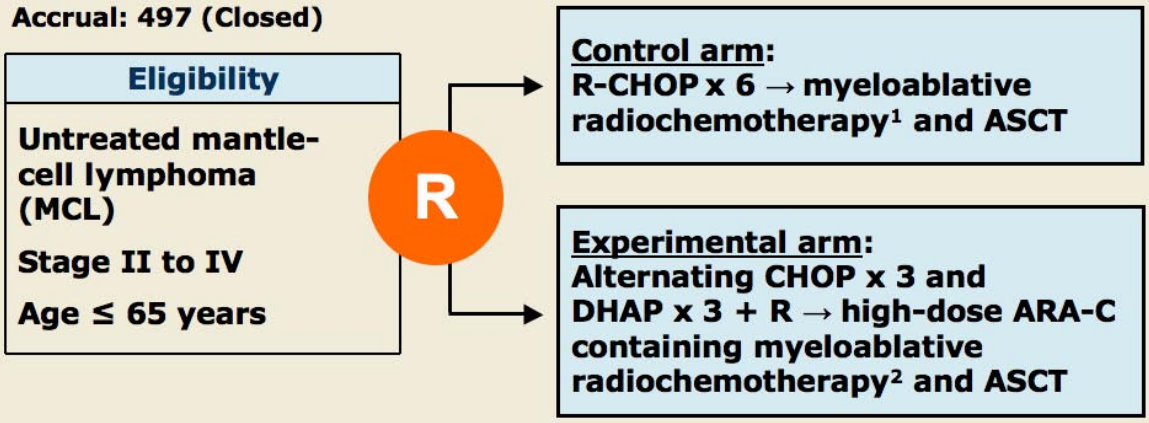
Background

- Although the outcomes of patients with MCL have improved over the last decades, the disease has been characterized by poor long-term prognosis.
- A Phase II trial of myeloablative consolidation followed by ASCT demonstrated significant prolonged progression-free survival in advanced stage MCL (*Blood* 2005;105:2677).
- Sequential R-CHOP/R-DHAP followed by ASCT demonstrated an overall response rate of 95% and a 75% survival rate at five years in a Phase II study of patients with MCL (*Proc ASH* 2008;Abstract 581).

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Study Schema



Primary endpoint: Time to treatment failure (TTF), monitored continuously.

[1] 12 Gray total body irradiation (TBI), cyclophosphamide 60 mg/kg x 2; [2] 10 Gray TBI, ARA-C 1.5 g/m^2 x 4, melphalan 140 mg/m^2

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Patient Characteristics

	Control arm	Experimental arm
Age, median	55 years	56 years
Male gender	78%	79%
Stage IV	85%	79%
B symptoms	43%	33%
ECOG >2	5%	5%
Elevated LDH	37%	38%
MIPI risk level (low/intermediate/high)	61%/25%/14%	62%/23%/15%

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Time to treatment failure	49 months	Not reached	0.0384*
3-year overall survival	79%	80%	0.74

*Mainly due to a lower number of relapses in the experimental arm after complete or partial response (control arm, 20%; experimental arm, 10%) as the rate of ASCT-related deaths during remission was similar in both arms (control arm, 3%; experimental arm, 4%).

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Response following induction			
Overall response	90%	94%	0.19
Complete response (CR)	26%	39%	0.012
CR/unconfirmed CR	41%	60%	0.0003

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Patients transplanted	72%	73%	—
Response following transplant			
Overall response	97%	97%	Not reported
Complete response (CR)	63%	65%	Not reported
Remission duration (All patients)	48 months	Not reached	0.047
Remission duration (Patients achieving CR)	51 months	Not reached	0.077

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Grade 3 or 4 Adverse Events (from Abstract)

	Control arm	Experimental arm
Induction regimen		
Anemia	8%	28%
Leucopenia	48%	75%
Thrombocytopenia	9%	74%
Renal toxicity	0%	2%
Conditioning regimen		
Mucositis	43%	61%

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Author Conclusions

- The use of high-dose ARA-C in addition to R-CHOP and ASCT significantly increases complete response rates and TTF compared to standard therapy.
  - CR: 26% vs 39% (p = 0.012)
  - CR/CRu: 41% vs 60% (p = 0.0003)
  - TTF: 49 months vs not reached (p = 0.0384; HR, 0.68)
- High-dose ARA-C plus R-CHOP followed by ASCT does not cause clinically relevant increases in toxicity.
- Based on these data, the new standard regimen for patients up to 65 years of age with MCL should contain high-dose ARA-C followed by ASCT.

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Research To Practice®

Investigator comment on alternating courses of 3x CHOP and 3x DHAP and rituximab followed by a high-dose Ara-C-containing myeloablative regimen as part of ASCT

Though the pretransplant OR rates are equal, the CR is significantly higher in the experimental arm with R-CHOP/R-DHAP induction. It is also interesting that even though both arms were equal in terms of OR and CR rates after transplantation, the time to treatment failure was improved in the arm with a high-dose Ara-C-containing myeloablative regimen. It tells us that all complete responses are not created equal.

I believe this trial provides additional information that a more aggressive therapy that includes high-dose Ara-C, in a younger patient, will get to the goal of a longer disease-free survival. Until we learn more about how to treat mantle-cell lymphoma with a curative intent, I believe this is an appropriate mode of approaching younger patients with MCL.

Interview with Lauren C Pinter-Brown, MD, January 7, 2011

Research
To Practice®