5 Minute JournalClub

Key ASH Presentations
Issue 6, 2011

R-CHOP-14 Followed by ICE Consolidation without Radiation Therapy for Primary Mediastinal B-Cell Lymphoma (PMBCL)

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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 OBJECTIVE

- Recognize the rationale for avoidance of local radiation therapy in PMBCL, and summarize outcomes achieved with induction R-CHOP followed by ICE consolidation alone.

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

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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
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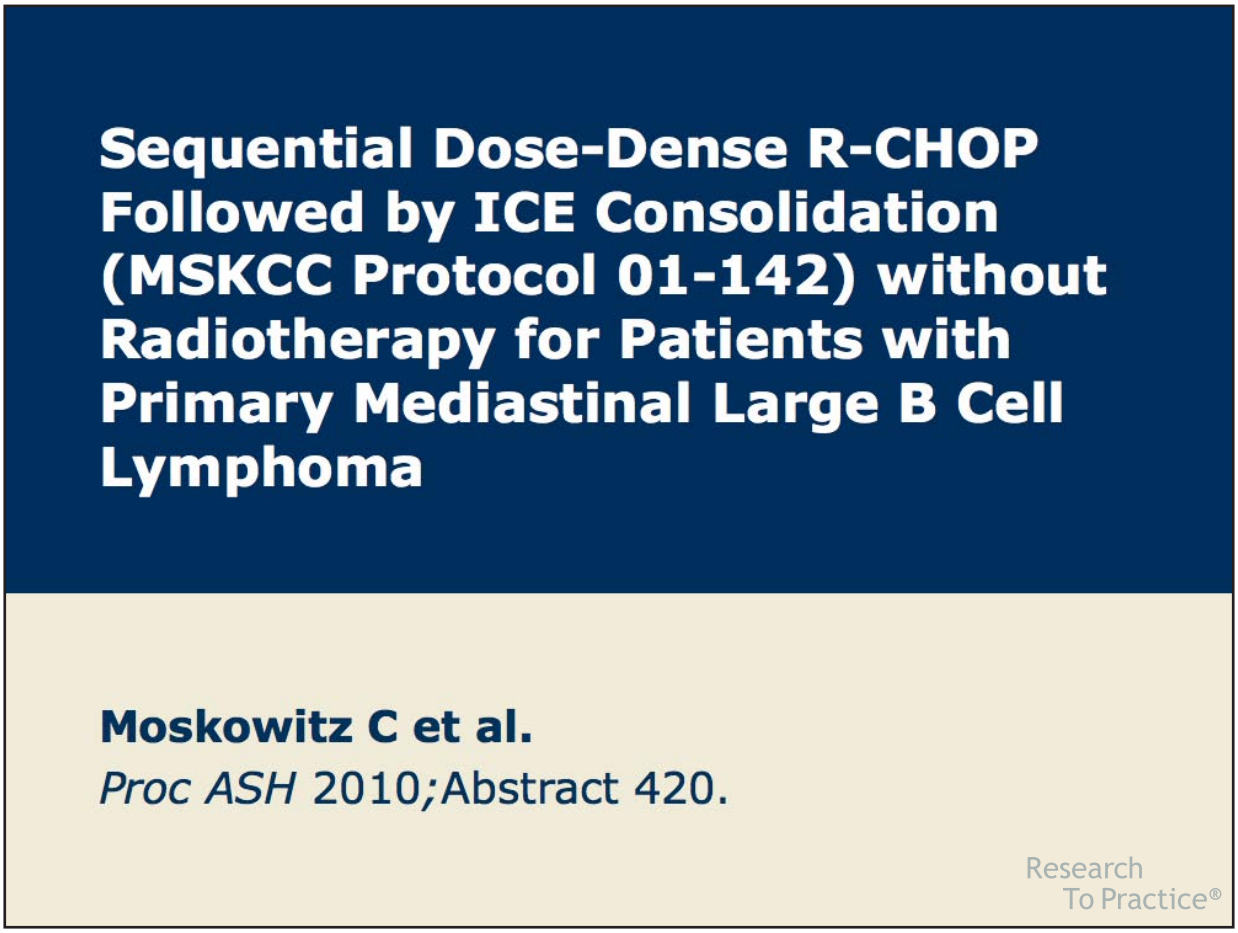
R-CHOP-14 Followed by ICE Consolidation without Radiation Therapy for Primary Mediastinal B-Cell Lymphoma (PMBCL)

Presentation discussed in this issue

Moskowitz C et al. **Sequential dose dense R-CHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal B cell lymphoma.** *Proc ASH* 2010;**Abstract 420**.

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



Background

- Primary mediastinal large B cell lymphoma (PMBCL) is a distinct subtype of diffuse large B cell lymphoma (DLBCL) that is more closely related to Hodgkin lymphoma.
  - More common in women
  - Median age ~ 30 years
  - Represents a high percentage of aggressive lymphomas in patients under 40 years of age
  - Bulky mediastinal disease is common
- Combined chemotherapy and radiation therapy have been the mainstay of treatment.
- Radiation therapy is associated with a risk of secondary breast cancer and coronary artery disease.
- Protocols that do not use radiation therapy are therefore desirable, provided they maintain efficacy outcomes.

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

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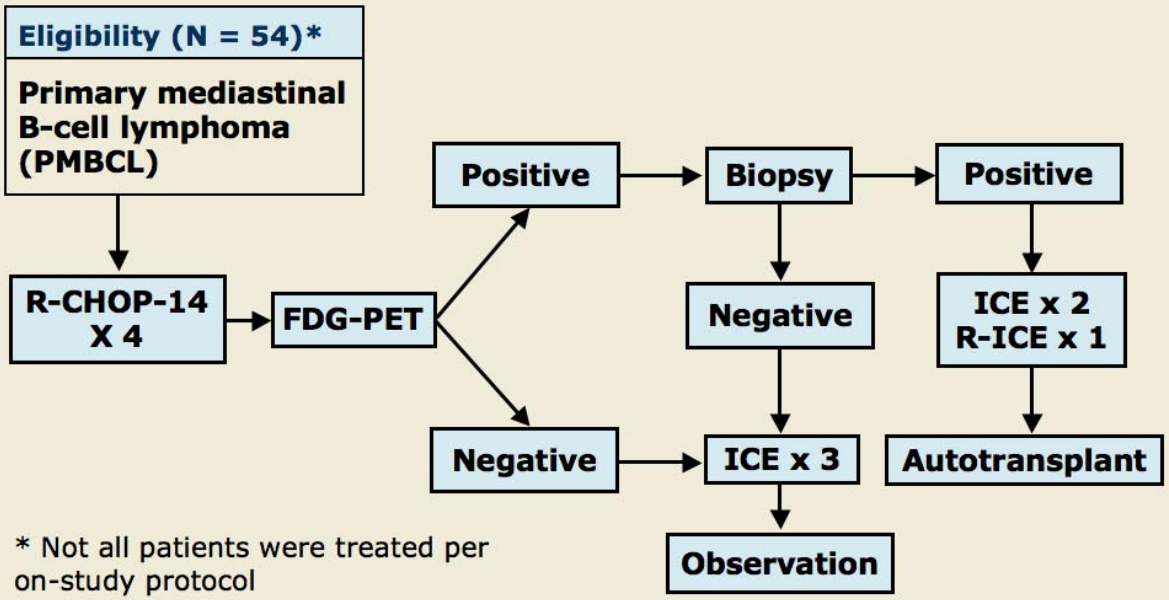
MSKCC 01-142 Study Schema: Primary Mediastinal B-Cell Lymphoma Subgroup



* Not all patients were treated per on-study protocol

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.
Moskowitz C et al. *J Clin Oncol* 2010;28:1896-903.

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Patient Characteristics

Characteristic	N = 54
Median Age	33
Female	56%
Elevated LDH	87%
Karnofsky Performance Status < 80%	24%
Stage IV Disease	57%
Extranodal Disease	74%
Bulky Mediastinal Disease ≥ 10cm	67%

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

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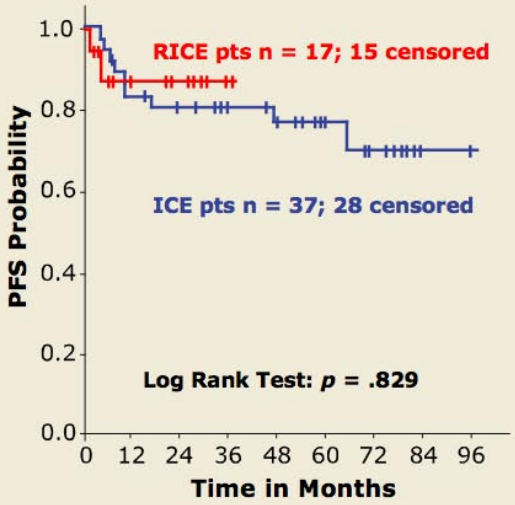
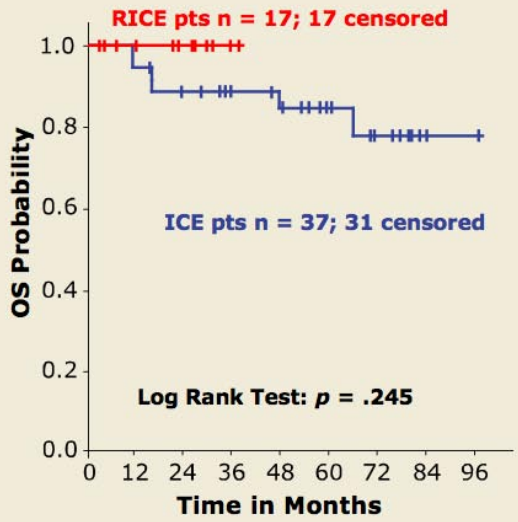
Survival: RICE versus ICE Consolidation

Progression Free Survival: RICE vs ICE



Overall Survival: RICE vs ICE



With permission from Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

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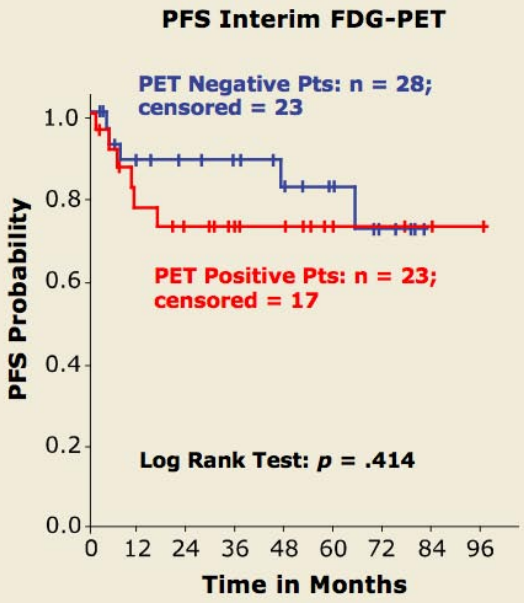
Interim FDG-PET

- 51/54 patients had an FDG-PET interim scan
- 23 patients had a +FDG-PET (SUV > 3.0)
  - All + scans had uptake > mediastinal blood pool
- 14 patients had a biopsy due to +FDG-PET
  - 11/14 had a negative biopsy
- Change in SUV between initial and interim scan (cutoff of >66% as being favorable) also did not predict outcome (p = 0.216)



With permission from Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Outcome of Patients with Events

- Eleven patients had an event after treatment
  - One patient died from AML (6 years post-treatment)
  - One patient was lost to follow-up — died of unknown causes (4 years post-treatment)
  - Nine patients have relapsed
    - Six patients received HDT/ASCT
      - Five patients are progression free after salvage therapy and autotransplant, which included pretransplant radiation to the mediastinum
      - One patient did not respond to ASCT and died of disease progression
    - Three patients died from PMBCL secondary to primary refractory disease

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Author Conclusions

- The MSKCC dose-dense R-CHOP/ICE program is highly effective in PMBCL.
- Importantly, 50% of patients with progression can be salvaged with a radiation-based transplant.
- Based on these results, an interim FDG-PET scan is not warranted as it provides no useful information in this subset of patients with DLBCL.

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Investigator Comment on Sequential Dose-Dense R-CHOP Followed by ICE Consolidation without Radiation Therapy for Patients with Primary Mediastinal Large B-Cell Lymphoma

This is a follow-up to the study that we published in the *JCO,* in which we treated advanced-stage diffuse large B-cell lymphoma in 98 patients and had an overall survival rate of 79 percent at a median of 44 months follow-up. This presentation is from patients with primary mediastinal large B-cell lymphoma (PMBCL) and is the largest study reported in this entity without consolidative radiation therapy.

Currently, most patients with PMBCL treated in the community receive R-CHOP followed by radiation therapy. Most physicians would prefer not to administer mediastinal radiation therapy, particularly to a young woman. This study shows that radiation therapy is not necessary and it could be reserved for patients who experience relapse. Treated this way, without initial consolidative radiation therapy, the issues of secondary breast cancer and long-term coronary artery disease could be prevented.

Interview with Craig Moskowitz, MD, January 3, 2011