5 Minute JournalClub

Key ASH Presentations
Issue 6, 2011

Lenalidomide/Dexamethasone as Salvage Treatment in Mantle-Cell Lymphoma (MCL)

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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

- Summarize the response rates and tolerability of salvage treatment with combination lenalidomide/dexamethasone in adult patients with relapsed or refractory MCL.

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Advisory Committee: Allos Therapeutics, Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium — The Takeda Oncology Company; Consulting Agreement: Millennium — The Takeda Oncology Company.

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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.

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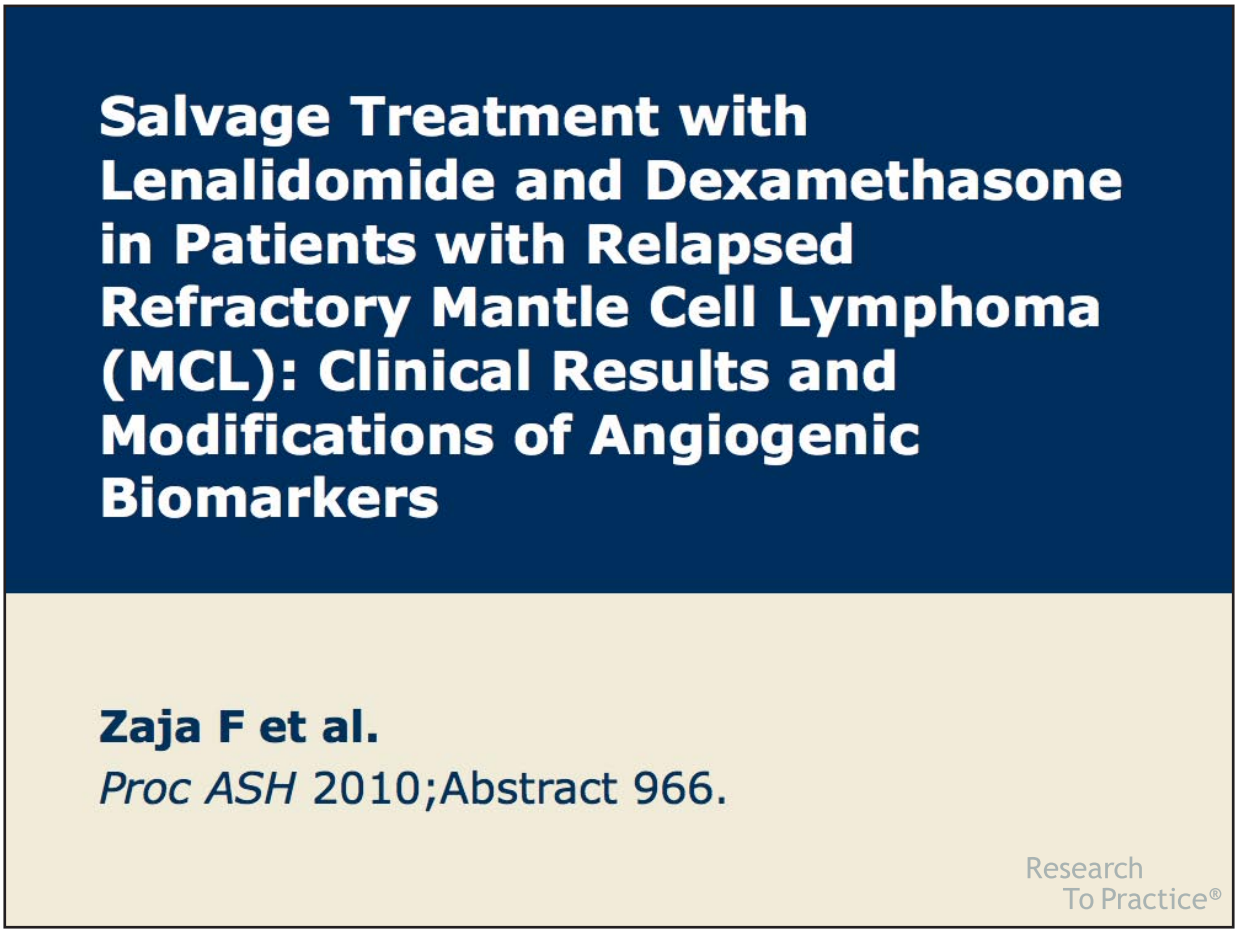
Lenalidomide/Dexamethasone as Salvage Treatment in Mantle-Cell Lymphoma (MCL)

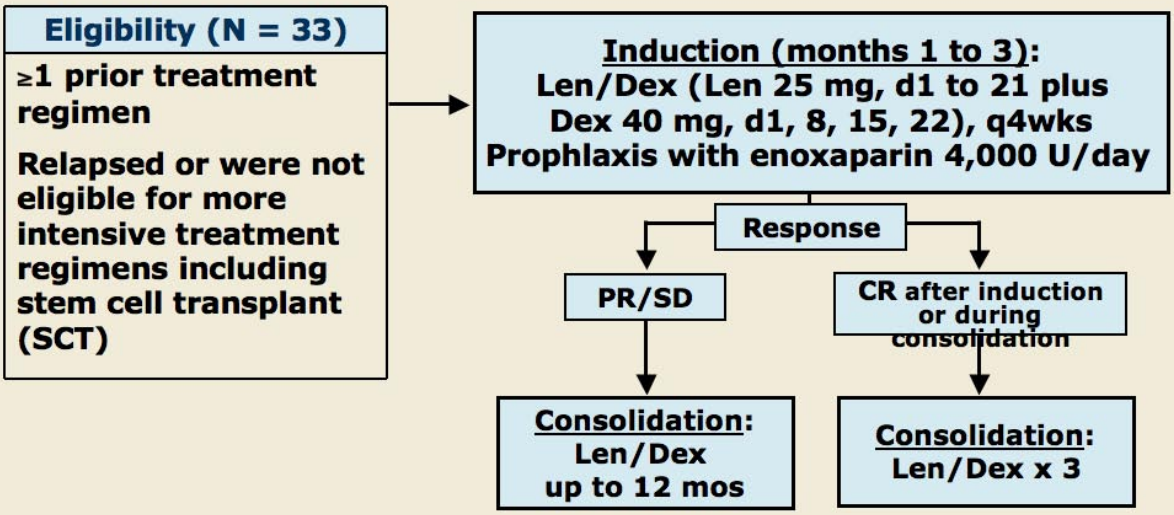
Presentation discussed in this issue

Zaja F et al. **Salvage treatment with lenalidomide and dexamethasone in patients with relapsed or refractory mantle cell lymphoma: Clinical results and modifications of angiogenic biomarkers.** *Proc ASH* 2010;**Abstract 966**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Bruce D Cheson, MD (12/23/10)



Phase II Study Schema



The objectives were to evaluate the safety and efficacy (overall response and complete response rates) of combination lenalidomide/dexamethasone (Len/Dex) in adult patients with MCL

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Patient Characteristics

	Len/Dex N = 33
Age, median	68 years (range 51-80)
Histology	
Classic	30
Blastoid	3
Prior treatments, median	3 (1-7)
Autologous SCT	12
Prior therapy with bortezomib	8

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Efficacy Results

Response following induction	Len/Dex N = 33
Overall response (OR)*	67%
Stable disease	3%
Complete response	15%
No response or progressive disease	30%

* 50% OR in patients previously treated with autologous SCT or bortezomib

Zaja F et al. *Proc ASH* 2010;Abstract 966.

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Efficacy Results

Final response status	Len/Dex N = 33
Overall response	52%
Complete response	24%
No response or progressive disease	45%
Median duration of response*	18 months
Survival	
Median overall survival	20 months
Median progression-free survival	12 months

After a median follow-up of 6 months from the end of therapy, none of the patients with CRs had subsequent progression whereas 2 patients with partial response had progression 7 to 10 months after therapy was completed.
* Median follow-up = 30 months

Zaja F et al. *Proc ASH* 2010;Abstract 966.

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Efficacy Results

- Angiogenic plasma biomarkers (ie, bFGF, VEGF, HGF) showed a trend to decrease after the first 3 months of therapy.
- Macrophage counts significantly increased after the first 3 months of therapy, in parallel with significant increases in microvessel counts.
  - Bone marrow counts ($P<0.01$)
  - Microvessel counts ($P<0.05$)
  - Both counts were always significantly correlated ($P<0.001$)

Zaja F et al. *Proc ASH* 2010;Abstract 966.

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Grade 3/4 Adverse Events

	Len/Dex N = 33
Neutropenia	52%
Thrombocytopenia	18%
Neutropenic fever	12%
Bacterial pneumonia	9%
Dyspnea	9%
Anemia	6%
Hypotension	3%

Zaja F et al. *Proc ASH* 2010;Abstract 966.

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Author Conclusions

- These data confirm the efficacy of Len/Dex in patients with relapsed or refractory MCL.
  - Final OR, 52%; CR, 24% (6-month follow-up)
- The safety profile of the Len/Dex combination was favorable.
- The significant infiltration of macrophages into the bone marrow may be due to an immunomodulatory effect of lenalidomide.
- The increased microvessel counts may be induced by activated macrophages, although angiogenic plasma biomarker concentrations suggest only a limited effect of lenalidomide on neovascularization.

Zaja F et al. *Proc ASH* 2010;Abstract 966.

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Investigator comment on lenalidomide/dexamethasone for relapsed or refractory mantle-cell lymphoma

Lenalidomide is interesting in mantle-cell lymphoma and has been associated with response rates of approximately 50 percent among patients with relapsed or refractory disease. The current study sought to improve on that by adding dexamethasone to the lenalidomide in a relatively small number of patients. An overall response rate of 67 percent was observed after induction, with 15 percent being complete remissions. Many of these responses also appear to be durable. Whether the addition of dexamethasone adds to the efficacy of lenalidomide would require a randomized trial.

Interview with Bruce D Cheson, MD, December 23, 2010

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