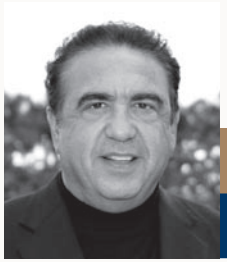


NEIL LOVE, MD

BACK WHERE IT ALL BEGAN

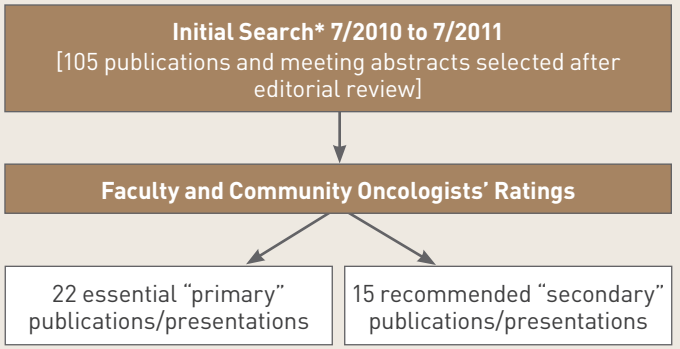
In early 2008, after the unprecedented data explosion at the 2007 American Society of Hematology (ASH) Annual Meeting where no fewer than 6 Phase III randomized trials in multiple myeloma were presented, our CME group sensed a great need for education in this challenging and unique disease. Within weeks we were swimming in previously uncharted waters as we attempted to conceptualize an educational resource that would expose practicing clinicians to these and other newly emerging trial results while also helping them to understand how this information should be applied to clinical practice. The result of this extensive investment of time and brainpower was not only our first major foray into multiple myeloma but also the creation of an entirely new educational format — *Year in Review*.

Since that time, 3 things have happened:

1. We have moved forward full force with myeloma education and have provided clinicians with an array of relevant perspectives on the disease.
2. We have successfully expanded *Year in Review* and have now produced similar editions focused on breast cancer, lung cancer, gastrointestinal cancer and non-Hodgkin lymphoma.
3. Multiple myeloma research has continued to outpace efforts in many other solid tumors and hematologic cancer.

To that end, we once again felt the need to "evaluate, distill and deliver," and as such we asked 3 clinical investigators and 10 oncologists in community-based practice to sift through the new mountain of information in multiple myeloma to determine what is most relevant to daily patient care. The 22 papers featured as "Primary" publications in this monograph/slide set are considered by our reviewers to be required reading for any physician providing care for patients with this disease. These are accompanied by brief comments from our faculty co-editors and 15 additional "Secondary" papers that are highlighted and annotated.

Process for Identifying Key Recent Reports on the Management of Multiple Myeloma



* PubMed July 22, 2010 through July 22, 2011. English language, clinical trials, controlled clinical trials, meta-analyses, practice guidelines, core clinical journals. Search of meeting abstracts from 2010 ASH, 2011 ASCO and International Myeloma Workshop 2011 annual meetings.

For us, this super-practical resource summarizes the latest chapter of progress that has been made in the field. But if history serves correctly, it is also another reminder that we are in the midst of a continually evolving story that gets better and more exciting each and every year.

— Neil Love, MD
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CLINICAL TRIAL RESULTS WITH APPROVED AGENTS

8 Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

10 McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB ECOG BMT-CTN 100104.** *Proc International Myeloma Workshop* 2011.

12 Attal M et al. **Maintenance treatment with lenalidomide after transplantation for myeloma: Analysis of secondary malignancies within the IFM 2005-02 trial.** *Proc International Myeloma Workshop* 2011.

14 Dimopoulos MA et al. **Lenalidomide and dexamethasone (LEN plus DEX) treatment in relapsed/refractory multiple myeloma (RRMM) patients (pts) and risk of second primary malignancies (SPM): Analysis of MM-009/010.** *Proc ASCO* 2011;Abstract 8009.

16 Bringhen S et al. **Efficacy and safety of once-weekly bortezomib in multiple myeloma patients.** *Blood* 2010;116(23):4745-53.

18 Moreau P et al. **Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study.** *Lancet Oncol* 2011;12(5):431-40.

20 Palumbo A et al. **A phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma (NDMM): Continuous use of lenalidomide vs fixed-duration regimens.** *Proc ASH* 2010;Abstract 622.

22 Goldschmidt H et al. **Bortezomib-based induction therapy followed by autologous stem cell transplantation and maintenance therapy with bortezomib improves outcome in myeloma patients with gain 1q21 and t(4;14) — A subgroup analysis of the HOVON-65/GMMG-HD4 trial.** *Proc ASH* 2010;Abstract 305.

24 Cavo M et al; GIMEMA Italian Myeloma Network. **Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study.** *Lancet* 2010;376(9758):2075-85.

26 Cavallo F et al. **Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy.** *Leukemia* 2011;25(10):1627-31.

28 Mateos MV et al. **Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial.** *Lancet Oncol* 2010;11(10):934-41.

30 Palumbo A et al. **Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT) for initial treatment of elderly multiple myeloma patients: Updated follow-up and impact of prognostic factors.** *Proc ASH* 2010;Abstract 620.

32 Niesvizky R et al. **Phase 3b UPFRONT study: Safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients.** *Proc ASH* 2010;Abstract 619.

34 Dimopoulos M et al. **The efficacy and safety of lenalidomide plus dexamethasone in relapsed and/or refractory multiple myeloma patients with impaired renal function.** *Cancer* 2010;116(16):3807-14.

MULTIPLE MYELOMA WORKUP AND RISK STRATIFICATION

36 Dimopoulos M et al; International Myeloma Workshop Consensus Panel 3. **Consensus recommendations for standard investigative workup: Report of the International Myeloma Workshop Consensus Panel 3.** *Blood* 2011;117(18):4701-5.

38 Munshi NC et al; International Myeloma Workshop Consensus Panel 2. **Consensus recommendations for risk stratification in multiple myeloma: Report of the International Myeloma Workshop Consensus Panel 2.** *Blood* 2011;117(18):4696-700.

NOVEL AGENTS UNDER INVESTIGATION

40 Leleu X et al. **Phase 2 study of 2 modalities of pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. IFM 2009-02.** *Proc ASH* 2010;Abstract 859.

42 Lacy MQ et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Blood* 2011;118(11):2970-5.

44 Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial.** *Proc ASH* 2010;Abstract 862.

BONE-TARGETED TREATMENT

46 Morgan GJ et al; National Cancer Research Institute Haematological Oncology Clinical Study Group. **First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): A randomised controlled trial.** *Lancet* 2010;376(9757):1989-99.

48 Boyd K et al. **Does zoledronic acid (ZOL) reduce skeletal-related events (SREs) and improve progression-free survival (PFS) in patients (pts) with multiple myeloma (MM) with or without bone disease? MRC Myeloma IX study results.** *Proc ASCO* 2011;Abstract 8010.

48 Davies FE et al. **Bisphosphonate treatment in multiple myeloma: Should they be used until progression?** *Proc ASCO* 2011;Abstract 8011.

SECONDARY PUBLICATIONS/PRESENTATIONS (RECOMMENDED)

CLINICAL TRIAL RESULTS WITH APPROVED AGENTS

1. Palumbo A et al. **Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) in newly diagnosed multiple myeloma (MM) patients: A phase III study.** *Proc EHA 16th Congress* 2011.

   The first reported study evaluating the role of ASCT versus induction therapy in the era of novel agents. A statistically significant PFS benefit was reported in patients with newly diagnosed multiple myeloma (NDMM) receiving MEL200 compared to MPR (18-month PFS: 78% versus 68%), although toxicities were significantly higher. No significant difference in OS was reported in the current analysis.

2. Harousseau JL et al. **Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: Results of the IFM 2005-01 phase III trial.** *J Clin Oncol* 2010;28(30):4621-9.

   VD significantly improved postinduction and post-transplantation CR, near CR and ≥VGPR rates compared to VAD and resulted in a trend for longer PFS in patients with NDMM.

3. Gay F et al. **Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma.** *Am J Hematol* 2010;85(9):664-9.

   In a retrospective analysis of 72 patients with NDMM, addition of clarithromycin to Rd appeared to significantly improve CR, time to disease progression and PFS outcomes.

4. Roussel M et al. **Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: Primary results of the IFM 2008 phase II study.** *Proc ASH* 2010;Abstract 624.

   VRD induction followed by ASCT and VRD consolidation produced high-quality responses and was well tolerated in patients with NDMM younger than age 65. ORR after ASCT was 94% (including 32% VGPR, 13% CR and 23% stringent CR).

5. Cavo M et al. **Bortezomib-based induction treatments improve outcomes of newly diagnosed multiple myeloma patients with high-risk cytogenetic abnormalities.** *Proc ASH* 2010;Abstract 781.

   In patients with NDMM receiving bortezomib-based induction treatments, del(13q) alone and del(17p) alone did not adversely influence PFS and OS. Presence of t(4;14) alone did not adversely influence PFS but was associated with a shorter OS. Presence of both del(17p) and t(4;14) was likely to confer a dismal clinical outlook.

6. Harousseau JL et al. **Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: Analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone.** *Blood* 2010;116(19):3743-50.

   An analysis of the prognostic effect of response on time-to-event parameters in the VISTA trial concluded that CR is an important treatment goal and supported prolonged VMP therapy to achieve maximal response.

7. Zonder JA et al. **Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: A randomized Southwest Oncology Group trial (S0232).** *Blood* 2010;116(26):5838-41.

   One-year PFS, ORR and VGPR were superior with RD versus dexamethasone, whereas 1-year OS was similar. Toxicities were more pronounced with RD, including Grade 3 neutropenia and thromboembolic events despite aspirin prophylaxis.

8 Kumar S et al. **Novel three- and four-drug combination regimens of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for previously untreated multiple myeloma: Results from the multi-center, randomized, phase 2 EVOLUTION study.** *Proc ASH* 2010;Abstract 621.

Continuous weekly C in the VDC regimen was associated with high response rates and rapid responses versus VDR and VDCR. VDCR did not result in a substantial increase in response rate and was associated with a modest increase in the incidence of hematologic toxicities.

9 Benevolo G et al. **The efficacy and safety of bortezomib and dexamethasone as a maintenance therapy in patients with advanced multiple myeloma who are responsive to salvage bortezomib-containing regimens.** *Cancer* 2011;117(9):1884-90.

Bortezomib and dexamethasone was effective (1-year ORR: 76%) and well tolerated as maintenance therapy in 49 patients with MM who were responsive to prior bortezomib-based salvage regimens.

10 Palumbo AP et al. **Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older.** *Proc ASCO* 2011;Abstract 8007.

Among patients with NDMM, an imbalance of AML incidence was observed in patients who received MPR/MPR-R versus MP, but incidence was low (0.7% versus 0%), and SPM risk was similar in other studies.

11 Rossi AC et al. **Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM).** *Proc ASCO* 2011;Abstract 8008.

No cases of secondary MDS/AML occurred among 68 patients with NDMM who received BiRD after 4 years.

12 Madan S et al. **Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma.** *Blood* 2011;118(7):1763-5.

The efficacy of re-treatment on relapse with lenalidomide was higher than re-treatment with thalidomide among 113 evaluable patients.

NOVEL AGENTS UNDER INVESTIGATION

13 Richardson P et al. **A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib.** *Proc ASH* 2010;Abstract 864.

Single-agent pomalidomide achieved clinically significant durable responses with a manageable safety profile in patients with heavily pretreated relapsed or refractory MM. Addition of dexamethasone can reinduce response in selected patients.

14 Siegel DS et al; Multiple Myeloma Research Consortium (MMRC). **PX-171-003-A1, an open-label, single-arm, phase (Ph) II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (R/R MM): Long-term follow-up and subgroup analysis.** *Proc ASCO* 2011;Abstract 8027.

In 257 response-evaluable patients with relapsed or refractory MM, single-agent carfilzomib resulted in an ORR of 24% and a median duration of response of 7.4 months. No new, unexpected or cumulative toxicities were observed, and adverse events were clinically manageable.

BONE-TARGETED TREATMENT

15 Henry DH et al. **Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *J Clin Oncol* 2011;29(9):1125-32.

Denosumab was noninferior (trending to superiority) to zoledronic acid in preventing or delaying first on-study SRE. ONJ occurred at similar low rates in both treatment groups.