

# R&DINSIGHTS

## Progress in Treating Newly Diagnosed Multiple Myeloma

By Ed Rabinowitz

The Office of Rare Diseases of the National Institutes of Health (ORD) defines a *rare disease* as typically having a prevalence “of fewer than 200,000 affected individuals in the United States.” Thus, ORD categorizes multiple myeloma, which afflicts approximately 20,000 Americans each year, as a rare disease; but for physicians involved in diagnosing and treating multiple myeloma, “rare” is relative.



David S. Siegel, MD, PhD

“It’s certainly not a rare disease in our office,” said David S. Siegel, MD, PhD, co-division chief, Division of Multiple Myeloma, The John Theurer Cancer Center at Hackensack University Medical Center in New Jersey. “For me, it’s an overwhelming disease. And in terms of its impact on the healthcare system, it’s an important disease.”

### Reassessing Transplant Timing

Dr Siegel and his colleagues have been actively involved in helping to develop new treatments for multiple myeloma. The John Theurer Cancer Center was among the institutions that brought bortezomib (Velcade) and lenalidomide (Revlimid) into wider clinical use. Initially used as single agents, they are now routinely used in combination with dexamethasone (the RVD regimen) and other drugs. According to IntrinsicQ, which captures monthly oncology data from clinical information systems used in academic medical centers, community hospitals, and private practices in the United States, bortezomib and lenalidomide accounted for 80% to 90% of myeloma treatments between October 2008 and September 2009.

“A decade ago we had probably two drugs that were active for the treatment [of multiple myeloma], and as we get more options, the combinations become more complex, as do some of the toxicities,” Dr Siegel said. “But, we’ve been fortunate as we’ve gotten new drugs in that many of them have better side effect profiles than the older drugs.”

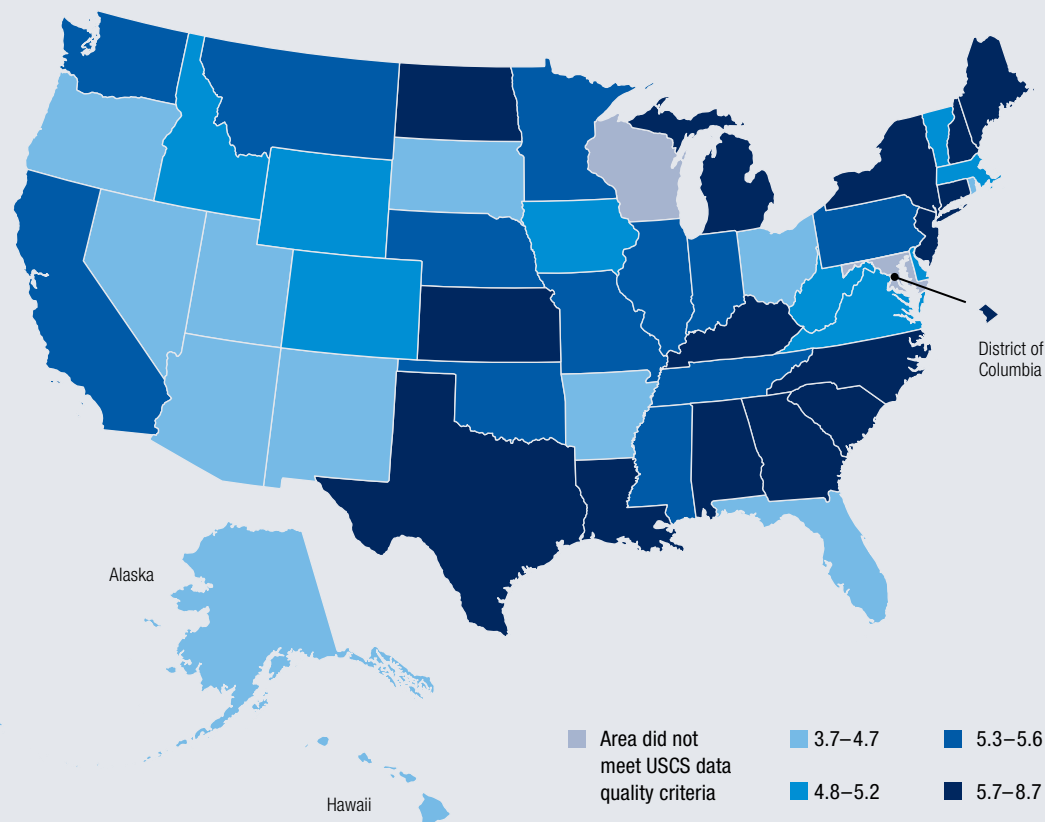
The center has also been an advocate of bringing myeloma patients to stem cell transplant earlier in the course of their disease. David H. Vesole, MD, PhD, co-division chief and director of research, Division of Multiple Myeloma at The John Theurer Cancer Center, said the question today is not whether to transplant but when to incorporate transplant into the treatment algorithm. He said,



**“If you give [patients] their initial therapy, and you transplant them for consolidation, that’s going to provide them with the longest disease control, and therefore the better quality of life.”**

—David H. Vesole, MD, PhD

### Incidence of Myeloma by State, 2005



Rates are per 100,000 and are age-adjusted to the 2000 US standard population.

Source: U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2005 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2009. Available at: <http://www.cdc.gov/uscs>.

given the new drug strategies that have emerged, the French Francophone Myeloma Intergroup (FFMI) decided to conduct an international trial to examine the optimal time for transplantation. US researchers are planning a similar trial to the FFMI study, but Dr Vesole said he does not expect data from the US study to be available for at least 5 years.

Until a wave of research indicates otherwise, Dr Vesole said he and his colleagues believe there is no reason to withhold transplant treatment early on. “You still get more benefits by having the transplants early as opposed to doing them later, as far as how long patients stay in remission,” Dr Vesole explained. “If you give [patients] their initial therapy, and you

transplant them for consolidation, that’s going to provide them with the longest disease control, and therefore the better quality of life, because they’ll be off drugs for a longer period of time.”

### New Drug Regimens: VDD & RVDD

Several institutions are looking at new combinations of existing drugs to treat newly diagnosed multiple myeloma and evaluating their effects on subsequent stem-cell transplantation. Data from a recently completed phase II trial published in the October 20, 2009, issue of the *Journal of Clinical Oncology*, led by Andrzej J. Jakubowiak, MD, PhD, University of Michigan, treated patients with newly diagnosed multiple myeloma using a combination of bortezomib, pegylated liposomal doxorubicin (PLD; Doxil), and dexamethasone (Decadron), a regimen referred to as VDD. Dr Jakubowiak and colleagues said they found the triplet “highly effective for initial treatment of multiple myeloma.” The rationale behind the trial came from prior clinical studies indicating that combinations of bortezomib with either PLD or dexamethasone “are well tolerated and appear more active than [bortezomib] alone.”

In the study, the overall response rate was 85.0%, with a very good partial response (VGPR) or better of 57.5%. In addition, the authors wrote, “Patients who underwent stem-cell transplantation (SCT)

after VDD experienced increased rates of VGPR or better (53.3%–76.6% after SCT). Overall, 1-year progression-free survival [PFS] and overall survival [OS] rates were 92.5% and 97.5%, respectively.” The investigators concluded that VDD is an active combination in patients with newly diagnosed myeloma. The regimen was also well tolerated, and researchers reported “limited occurrence of grades 3 or 4 adverse events.”

Dr Jakubowiak and colleagues have also been investigating a novel 4-drug regimen for treating newly diagnosed multiple myeloma that comprises lenalidomide, bortezomib, PLD, and dexamethasone, referred to as RVDD. RVD and VDD are very active regimens in newly diagnosed multiple myeloma and preclinical studies suggested combining the two might prove even more effective.

Dr Jakubowiak presented data from a phase I/II study at the 51st American Society of Hematology (ASH) Annual Meeting & Exposition, which found that the RVDD regimen was well tolerated and highly active in the 57 patients evaluable for response. Partial response was 96%, which included the 58% of patients with VGPR or better. All the patients who completed at least 4 cycles of the maximum tolerated dose, identified as 25 mg of lenalidomide, 1.3 mg/m<sup>2</sup> of bortezomib, 20 mg of dexamethasone, and 30 mg/m<sup>2</sup> of PLD, demonstrated partial response or better. At a median of 6 months’ follow-up, PFS and OS had not been reached (ASH Abstract 132).

### Personalizing Drug Therapy

At George Mason University’s Center for Applied Proteomics and Molecular Medicine in Fairfax, Virginia, clinicians are working with oncologists at Fairfax-Northern Virginia Hematology Oncology to study the effects of drug treatments on proteins in living tumor cells obtained from myeloma patients. In a trial called Ex Vivo Multiplexed Signal Pathway Inhibitor Treatment of Multiple Myeloma Bone Marrow Aspirates, the team is using a first-of-its-kind drug target mapping technology that creates a unique profile—or fingerprint—of which drug targets are activated in each patient’s tumor. Lance Liotta, MD, and Emmanuel Petricoin III, MD, co-directors of the center, are gathering data toward the goal of tailoring treatment for



Lance Liotta, MD



Emmanuel Petricoin III, MD

each patient based on the unique characteristics of the patient’s myeloma tumor cells. The trial started a year ago, and it may be completed by year-end 2009.

“The signaling activation of one patient’s tumor may look very different from the signaling activation of another patient’s tumor,” Dr Petricoin explained. “Under the microscope they may look the same. But in fact, when you look at the molecular signatures that we’re finding, it’s no wonder why the one-drug-fits-all-approach does not work.”

According to Dr Liotta, this is the first trial to examine the signaling pathways and how they are disrupted by targeted molecular inhibitors in living cells. In addition, never before have the myeloma cells and the normal non-myeloma cells been treated with the same inhibitor and compared. “In this way we preserve the potential interaction between the cell types, yet we can look individually at whether the drug is affecting the myeloma cells to a greater degree, or causing some end points to go up or down following treatment in the myeloma cells and not in the normal cells.”

The trial has been using a panel of molecular targeted inhibitors, including sunitinib (Sutent), dasatinib (Sprycel), and erlotinib (Tarceva), and the chemotherapeutics dexamethasone and rapamycin (Sirolimus), as well as collaborating with pharmaceutical companies on phase I compounds.

### More People Living with Multiple Myeloma

Dr Siegel said 20 years ago, approximately 10,000 new cases of multiple myeloma were diagnosed each year and about 50,000 patients were living with the disease. Despite progress, or more aptly, because of progress in diagnosing and treating multiple myeloma, those numbers have doubled.

“When I first started as a fellow taking care of myeloma patients, professors used to say that life expectancy for a myeloma patient who was requiring therapy was measured in months,” Dr Siegel said. “Now, it’s measured in years or decades. It used to be unheard of that we had a patient who was alive 20 years after diagnosis. Now, doctors say that happens routinely. But these 100,000 patients who live for another 10 years will require care for the entirety of those years. As a result, it’s disproportionately impactful on the healthcare system.” This is one more reason why researchers continue to search for treatments and drug regimens that will lead to better quality of life and hopefully a cure for multiple myeloma. **OBTN**

## Clinical Trials in Multiple Myeloma

### Cyclophosphamide, Bortezomib, Liposomal Doxorubicin, & Dexamethasone

This interventional phase I/II study, taking place in Florida, seeks to determine whether adding cyclophosphamide to the standard regimen of bortezomib (Velcade), pegylated liposomal doxorubicin (Doxil), and dexamethasone (Decadron) will be well tolerated and improve response rates in 108 adult patients with newly diagnosed multiple myeloma. Phase I of the study will identify the maximum tolerated dose of cyclophosphamide, and the primary endpoint for phase II is objective response rate (complete responses plus partial responses) with the CVDD regimen. Investigators will also be looking at time to first response, duration of response, progression-free survival (PFS), and overall survival.

**ClinicalTrials.gov ID:** NCT00750815

**Sponsor:** H. Lee Moffitt Cancer Center and Research Institute

**Principal Investigator:** Melissa Alsina, MD

**Contacts:** Kendra Anderson, RN, (813) 745-384, kendra.anderson@moffitt.org; Kara Kosakowski, (813) 745-5758, kendra.anderson@moffitt.org

### Thalidomide & Prednisone after Autologous Stem Cell Transplantation

This randomized phase III trial is studying thalidomide (Thalomid) and prednisone to see how well they work compared with observation alone in treating patients who have undergone stem cell transplantation for multiple myeloma. One arm will receive oral thalidomide daily and oral prednisone every other day for 4 years in the absence of disease progression or unacceptable toxicity. The other arm will receive no intervention but will be observed and assessed regularly for quality of life and progression. The study will accrue 324 patients over 3.5 years and is taking place at 38 sites in the United States and Canada, with several in Michigan.

**ClinicalTrials.gov ID:** NCT00049673

**Sponsor:** NCIC Clinical Trials Group

**Principal Investigators:** A. Keith Stewart, MD, and Philip R. Greipp, MD

**Contacts:** See trial listing

### Lenalidomide with or without Dexamethasone

In this phase II study, investigators from the Mayo Clinic in Rochester, Minnesota, will be accruing 39 patients with newly diagnosed, untreated multiple myeloma. The study is open label, and patients will receive up to 18 courses of lenalidomide (Revlimid) alone, with dexamethasone (Decadron) added beginning with course 4 for those who demonstrate disease progression or fail to respond. The primary objective is to assess PFS at 1 year, with secondary objectives of response and toxicity.

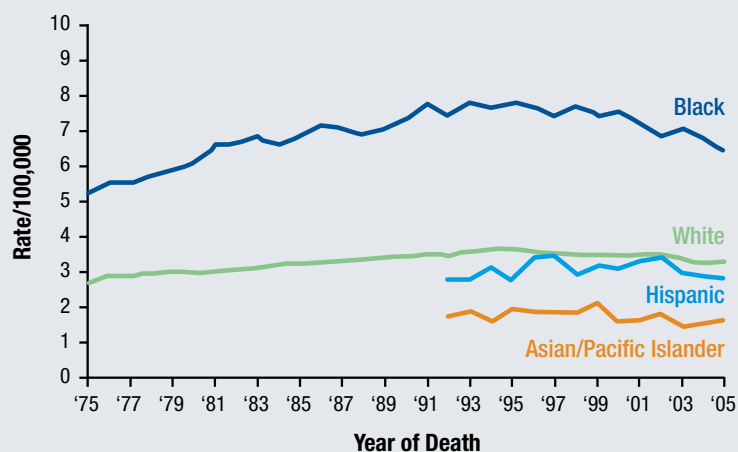
**ClinicalTrials.gov ID:** NCT00772915

**Sponsor:** Mayo Clinic, National Cancer Institute

**Study Chair:** Shaji K. Kumar, MD

**Contacts:** Clinical Trials Office, (507) 538-7623

### US Deaths from Myeloma by Race and Ethnicity, 1975–2005



Mortality source: U.S. Mortality Files, National Center for Health Statistics, CDC.