

# Poly-MVA in an Integrative Approach to the Treatment of Multiple Myeloma: A Case Report

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*Townsend Letter; Aug/Sept 2007 issue*

## **Abstract**

Multiple myeloma remains one of the deadliest forms of cancer with a poor prognosis, regardless of treatment. Complete remission is uncommon and a cure is rare. Only one percent of the patients diagnosed with this disease are younger than 40 years of age; at least half are over 71. This article describes a remarkable case of a 67-year-old man, diagnosed in 2001 with end-stage multiple myeloma, who was only offered palliative care and told to admit himself into hospice with three months to live. This case report describes his recovery using an integrative approach with an unconventional dosing of chemotherapy along with a dietary supplement.

## **Introduction**

Multiple myeloma is a relatively uncommon cancer. The American Cancer Society estimates that approximately 16,000 new cases of multiple myeloma were diagnosed in 2005; multiple myeloma was expected to kill over 11,000 Americans last year. The five-year relative survival rate for multiple myeloma is 32 percent higher in younger people, and lower in the elderly. The five-year survival rates cited here are based on patients diagnosed and initially treated more than five years ago.<sup>1</sup> The five-year survival rate refers to the percentage of patients who live at least five years after their cancer is diagnosed; five-year relative survival rates exclude patients dying of other diseases. Age is the most significant multiple myeloma risk factor, with one percent of cases diagnosed in individuals younger than 40; at least half of those diagnosed are over age 71. Men are 50 percent more likely than women to be diagnosed with multiple myeloma.<sup>1</sup>

While the website of the American Cancer Society<sup>1</sup> claims there are improved methods of treatment, the facts are that complete remission is uncommon and a cure is rare.<sup>2</sup> Patients who receive either allogenic or autologous stem cell transplants for multiple myeloma have a similar 3-5 year survival. While there is some suggestion that allograft, tandem autologous transplants, or nonmyeloablative allogenic transplants may reduce the high transplant related morbidity and mortality, nothing thus far has truly impacted the overall relapse and survival of this disease.<sup>2,3</sup> In any event, older patients (>65 years) are not candidates for transplantation.<sup>4</sup> Most patients receive intensive chemotherapy, which is associated with severe toxicity contributing to morbidity and mortality. In a meta-analysis of data from 575 patients with multiple myeloma comparing either high-dose chemotherapy or conventionally dosed chemotherapy, there was no statistically significant difference in long-term survival. However, high-dose chemotherapy followed by autologous stem cell transplantation delayed time to relapse by 14.5 months, but not survival time.<sup>5</sup> Other treatments are summarized in the next section; information was taken directly from the American Cancer Society's website.<sup>1</sup>

### **Conventional Treatment for Multiple Myeloma**

Thalidomide is a drug that was originally developed as a sedative and banned because it caused birth defects, but it is now being used to treat multiple myeloma. Thalidomide is an immunomodulator and may also inhibit angiogenesis, possibly reducing or preventing the growth of cancer cells. When thalidomide is combined with a corticosteroid dexamethasone, about 70 percent of patients have a partial or complete disappearance of their myeloma; although, it is temporary in virtually all patients and no clear data indicates extension of survival. Thalidomide has significant side effects, including severe constipation, numbness and tingling of extremities (neuropathies), fatigue, and sleepiness. Except for the sleepiness, symptoms become worse the longer the drug is given. Although new drugs, similar to thalidomide but with fewer side effects, have been developed and are making their way into clinical use, they have not impacted on survival time.<sup>1</sup>

Bortezomib (Velcade<sup>®</sup>), previously known as PS-341, was recently approved by the FDA for use in patients whose multiple myeloma has progressed after at least two prior forms of treatment. Bortezomib is a new type of drug known as a proteasome inhibitor. It works by stopping enzyme complexes (proteasomes) in cells from breaking down proteins important for keeping cell division under control. It appears to affect tumor cells more than normal cells and was approved based on evidence from two early clinical studies that showed it could shrink tumors in about one third of the patients who received it. Larger studies are now underway to determine if it prolongs survival and if it might be useful earlier in the course of the disease. The most common side effects include nausea and vomiting, fatigue, diarrhea, constipation, decreased platelet count (causing easier bruising and bleeding), fever, and decreased appetite. Bortezomib also caused some cases of peripheral neuropathy.<sup>1</sup>

Bisphosphonates may be used for symptom relief, an important goal of treatment. The symptoms of greatest concern to many individuals with myeloma are those due to bone damage. The myeloma cells can actually cause bone to dissolve, leading to brittleness and fracture of bones; bisphosphonates can slow down this process.

The standard bisphosphonates for treating bone problems in multiple myeloma, pamidronate or zoledronic acid (Zometa<sup>®</sup>), are given intravenously. Many doctors recommend that treatment with a bisphosphonate begin along with chemotherapy treatment in those with bone involvement.<sup>1</sup>

External beam radiation is used for treating multiple myeloma or solitary plasmacytoma. Having radiation therapy is much like having a diagnostic x-ray except that each treatment lasts longer and is usually repeated several times weekly for several weeks. There is no data that radiation of any kind extends remission time or overall survival statistics in multiple myeloma.<sup>1</sup>

In a thorough review of all the available treatments for this disease the conclusions can be summed up as follows:

1. No treatment has impacted the 3-5 year survival rates.
2. Most treatments are limited because they are toxic and can result in morbidity and mortality.
3. The quality of life during treatment is poor.
4. Relapse from any conventional treatment is inevitable.
5. With some treatments, such as autologous transplants, complete remission and progression-free survival rates are similar to other treatments, but overall median survival may be lower.
6. Newer drugs such as bortezomib are considered as a last resort in myeloma because of modest efficacy and major risks.<sup>6</sup>

The following is a case report of a patient diagnosed with multiple myeloma who at 67 years of age was not a candidate for any type of transplant. He refused conventional chemotherapy, opting to try low-dose thalidomide with dexamethasone and seek alternative cancer therapy that would hopefully improve survival and quality of life. He used Poly-MVA<sup>®</sup>, a dietary supplement as an integrative protocol as part of his treatment.

### **Poly-MVA and Mechanism of Action**

Poly-MVA is a proprietary formulation that contains palladium, alpha-lipoic acid, thiamine, riboflavin, cyanocobalamin, formyl-methionine, and N-acetylcysteine. Its main active ingredient is a lipoic acid/palladium complex (LAPd) that is sold as a dietary supplement and is being considered by the pharmaceutical industry under several patents<sup>7</sup> as “synthetic reductase.” The initials “MVA” stand for “minerals, vitamins and amino acids.” LAPd complex has undergone extensive toxicology study,<sup>8</sup> both intravenously and orally. Mice were administered doses of 5,000 mg/kg (a typical human dose is 20 mg/kg). Because no deaths or signs of organ damage occurred in the test animal, it was concluded that the LD<sub>50</sub> of LAPd exceeds 5,000 mg/kg. The same independent lab conducted an Ames test, which was negative.

LAPd was also studied for its effectiveness in halting the growth of glioblastoma cells *in vivo*.<sup>9</sup> Glioblastoma tumor cells were injected into the neck of Swiss nude mice. When the tumors had grown to 200-400 mm, the mice were divided into eight groups of 10. Four groups were given daily intravenous doses of either LAPd or placebo; four groups were given intraperitoneal LAPd or placebo. Those who were given LAPd received doses of 1.0, 1.5, 2.0, or 2.5 mg per mouse for a total of four weeks. At the end of four weeks, tumor volume was assessed. All of the mice receiving LAPd intravenously or intraperitoneally had significant reduction in tumor size (50% or more) compared to those who received the placebo. Dosages of 1.0-2.0 mg are comparable to those dosages used in humans adjusted for body weight.

Poly-MVA's proposed mechanisms of action are directly related to its structural formulation. It consists of an irreversibly-bound trimer of lipoic acid and palladium with a thiamine core. This complex is a liquid crystal polymer rather than a single molecule, which allows it to more efficiently provide a unified redox (accept charge and donate charge) effect. When glucose enters a cell it is broken down, in the absence of oxygen,

into pyruvate, which subsequently enters the mitochondria and is quickly oxidized to acetyl-coenzyme A (acetyl-CoA). In aerobic respiration, acetyl-CoA is then channeled into the Krebs/citric acid cycle to create the reduced form of nicotinamide adenine dinucleotide (NADH). NADH donates its electron to the electron transport chain to drive the phosphorylation of adenosine triphosphate (ATP). The energy needs of the body are supplied by splitting ATP into adenosine diphosphate (ADP) and a free phosphate molecule. LAPd was created to shunt electron energy from itself to DNA and thus replace the electrons lost in normal cells as a result of the oxidative damage associated with radiation and chemotherapy.<sup>7-9</sup>

Studies have demonstrated that LAPd provides electrons to DNA via the mitochondria.<sup>7-9</sup> This electron transfer provides an additional energy source to normal cells. However, cancer cells are metabolically challenged and function in a hypoxic environment. Since excess electrons have less oxygen to accept them in the cancer cell, a local generation of free radicals occurs at the mitochondrial membrane. This activates apoptosis by facilitating the release of cytochrome C from the inner mitochondrial membrane, allowing the formation of an apoptotic complex in the cytoplasm. This complex results in the subsequent activation of the caspase cascade of enzymes that destroy the malignant cells. Given that healthy cells are richly oxygenated, LAPd is nontoxic to them and they actually benefit from the energy boost.

Recent findings have focused on the role of Poly-MVA and the potential of a malignant cell to physiologically adapt to a hypoxic environment. These physiological changes are mediated by a molecule called hypoxia inducible factor-1 (HIF-1), which increases in hypoxic conditions to promote an increase in vascular endothelial growth factor (VEGF, a promoter of angiogenesis); glucose transport 1 (GLUT1); glycolytic enzymes (critical components in anaerobic respiration); and erythropoietin (EPO; responsible for the differentiation of red blood cells).<sup>10</sup> Poly-MVA appears to decrease the production of HIF-1, thus restricting the ability of the cell to adapt to its environment and subsequently making it more vulnerable to apoptotic cell death.<sup>11</sup>

### **Case Study**

KW, a 67-year old male was diagnosed with advanced multiple myeloma in March 2001. His CT chest scan with contrast revealed multiple rib lesions and osteolytic lesions of the thoracic spine consistent with osseous metastatic disease. There was volume loss with pleural thickening and parenchymal scarring in the lower lung zones. Small pleural plaque was also seen posteriorly on the right. Focal mass within the lung was suspicious for malignancy. An additional mass involving the right lower ribcage appeared to be in the ninth rib. The mass which appeared to be destroying the rib, measured approximately 2 cm in maximum transverse diameter and extended over a segment 6 cm along the axis of the rib cage. His ninth rib as it abuts the manubrium had a lesion of 2.5 cm transverse that extended 5-6 cm within the rib. There were additional lesions from the rib into the lateral aspect of the T3 vertebra and other areas of lucency seen within the thoracic vertebral bodies that were also suspicious for osteolytic metastases.

KW was admitted into the hospital March 24, 2001 for diagnostic testing and was found to have a markedly elevated serum protein (9.9 g/L), reduced serum albumin (2.3 g/dL), very high gamma globulin (7.6 g/dL), and a high sedimentation rate (49 mm/hour), all of which are common with multiple myeloma. Serum protein electrophoresis showed a monoclonal protein band in the gamma region with decreased polyclonal immunoglobulins consistent with multiple myeloma. His monoclonal protein at time of diagnosis was 4 g/dL. A bone scan revealed the left humerus suspicious for a metastatic lesion; several metastases to the skull; suspicion of metastasis to the right femur, with a lesion in the proximal cortex laterally; and suspicion of metastasis to the left femur, with evidence of two small lesions of the proximal one-third of the femoral diaphysis.

KW was offered VAD chemotherapy (vincristine, adriamycin, doxorubicin). He was told that this treatment is not curative but would hopefully slow the progression of disease, especially the skeletal lesions that would ultimately lead to fractures. He was already experiencing significant bone pain. The bisphosphonate Aredia<sup>®</sup> (generic is pamidronate) was administered every 28 days by infusion to slow the skeletal involvement. KW was also offered another option of thalidomide/dexamethasone. KW wanted to research these treatments on his own and would later make a decision. His oncologist informed him he had approximately 90 days to live and suggested that he get his affairs in order, arrange hospice care, and start making funeral arrangements. He adamantly refused any chemotherapy.

KW started taking MGN-3, an extract of arabinoxylan from rice bran, (Lane Labs USA, Allendale, NJ) in April of 2001. He stopped taking it two months later when he witnessed no change. As of July 9, 2001, there had been no positive change in his condition, as evaluated by his oncologist. No conventional treatments had been tried since he had eschewed VAD chemotherapy. He started a loading dose of Poly-MVA (8 tsp daily) on July 9th, and continued on this loading dose for five months. At this same time he also started taking thalidomide 250 mg per day. After two days, he discontinued thalidomide due to side effects of a rash, circulatory disturbances, and severe muscle and bone pain. After several weeks he tried a lower dose of 50-100 mg of thalidomide per day as tolerated plus a small dose of dexamethasone, three 4-mg tablets per day (the therapeutic dose is 10 4-mg tablets per day). He also tolerated Aredia which he took each month. He continued his low, unconventional dose of thalidomide and dexamethasone and also continued taking Poly-MVA. In November 2001 he was re-evaluated by his oncologist. His monoclonal protein levels fell below 2 g/dL, indicative of full clinical remission, according to his oncologist. His oncologist said he had never seen a response this dramatic in a patient with advanced stage 4 multiple myeloma.

In December of 2001, KW lowered the dose of Poly-MVA to a maintenance dose of 2 tsp twice daily while continuing the thalidomide/dexamethasone at the low dose of 50 mg thalidomide once daily for 7-10 days of each month with or without a small dose (12 mg) of the dexamethasone as needed. He and his oncologist determined when to take the medications based on the evaluation of his monoclonal protein levels. If they stayed below 2.4 g/dL, he didn't take either thalidomide or dexamethasone. However, if they went above 2.4 g/dL he resumed the thalidomide 50 mg daily for 7-10 days in the month

and the blood test was repeated. If the levels were much greater than 2.4 g/dL, he took up to 100 mg of thalidomide for several of the 7-10 days and added dexamethasone if monoclonal protein levels were trending upward. The Poly-MVA apparently allowed him to reduce the thalidomide and dexamethasone doses to a more tolerable level that could be taken intermittently with virtually no side effects. KW discontinued Poly-MVA for three months from September to November 2001 to determine its effect on his treatment and because he was on vacation. After discontinuation, his monoclonal proteins rose to 5.5-6.0 g/dL from a level below 2.0 g/dL in September 2001. Upon resuming the Poly-MVA at the maintenance dose of 4 teaspoons daily, his monoclonal protein levels substantially decreased to 2.0-2.4 g/dL during the period of December 2001 through May 2003.

While KM was on a maintenance dose of 4 tsp daily (rather than the loading dose of 8 teaspoon per day) his monoclonal proteins never returned to the low level of 2.4 g/dL or less. In April of 2004 he began to take the Poly-MVA even less consistently (approximately 1-2 tsp, 2-3 times per week) and his monoclonal protein began to rise further. While peaks and valleys are observed, his monoclonal protein level did not decrease to the levels observed while on the maintenance or loading dose of Poly-MVA (at or below 2.4 g/dL), despite the fact that he was taking thalidomide (50-100 mg) and dexamethasone (12 mg) once per month for a period of 7-10 days.

During late September 2005, KW resumed a loading dose (8 tsp daily) of Poly-MVA in an attempt to lower his monoclonal protein levels to those obtained in early 2002. However, during this four-week period he had suspended taking his thalidomide and dexamethasone completely. His monoclonal protein level rose substantially to 7 g/dL by November of 2005. His laboratory results revealed marked erythrocyte hemolysis, indicative of end-state multiple myeloma. He felt extremely sick and his concerned oncologist admitted him to the hospital on November 28, 2005. He was hospitalized for two days and was started on the full therapeutic dose of thalidomide (250 mg) and dexamethasone (40 mg). He continued Poly-MVA (8 tsp daily) during his stay in the hospital and was able to tolerate the higher dose of the drugs, which he was unable to do when he was first diagnosed and treated. He was visited by hospice and released. After being released, he continued taking the medications at his unconventional dose of 50-100 mg thalidomide and 12 mg of dexamethasone (10-day regimen) while continuing the Poly-MVA (8 tsp/day). By January 2006 his monoclonal proteins plummeted to 2.3 g/dL. This seems to substantiate the synergistic relationship of this integrative treatment approach. He has continued on the loading dose of Poly-MVA and his specific regimen of thalidomide and dexamethasone per the results of monoclonal protein analysis. When his monoclonal proteins rise (he tests them each month) he adds 50-100 mg of thalidomide and 12 mg of dexamethasone for 7-10 days. During his January 2006 visit with his oncologist he exclaimed that he felt "terrific" and had virtually no pain; he still continues his monthly Aredia treatments. KW's oncologist completely supports the integrative approach he has chosen to take and is delighted at his patient's remarkable recovery.

Since being diagnosed with stage 4 advanced multiple myeloma approximately six years ago, the patient has changed to a predominantly organic diet, removed all mercury fillings, removed two root canals, and avoids the use of toxic products in or around the house (e.g., cleaning fluid, pesticides, etc.). He remains physically active, travels whenever he chooses, and has an excellent quality of life. As of the submission of this case study, KM still remains in excellent health and his monoclonal proteins are still monitored each month. If they rise slightly above 2.4 g/dL he takes the thalidomide and dexamethasone at his unconventional dose for 7-10 days per month and they quickly go below this number.

### **Discussion**

This case demonstrates a dramatic response to integrative cancer therapy with Poly-MVA, thalidomide, and dexamethasone. KW was only able to tolerate an unconventional low dose of thalidomide and dexamethasone for a maximum of a 10-day course, dependent on the results of monoclonal protein levels. When he was not taking the loading dose of Poly-MVA with his regimen of thalidomide and dexamethasone, his monoclonal proteins rose substantially. His monoclonal protein levels fell at or below 2.4 g/dL only when he was taking the loading dose of Poly-MVA with his medication. This case provides compelling evidence of a synergy between a dietary supplement and a chemotherapeutic regimen, resulting in the remission and stabilization of this patient and keeping him alive and well for almost six years. This patient continues to be closely monitored by his oncologist and his ongoing progress will be reported as a follow up in other case reports. As of the publication of this case study, KW still remains alive and well and considered in full remission. Further research is greatly needed to elucidate the best possible outcome for the use of Poly-MVA in conjunction with a variety of cancer therapies for different forms of cancer.

**Addendum:** KW died on November 9, 2006. Prior to the spring of 2006, KW started to feel very tired and needed to sleep during the day. He had continued the thalidomide, however prior to the spring of 2006 he had stopped taking the Poly-MVA regularly again. His red blood cell count became extremely low and he required several transfusions during the spring of 2006. His physician prescribed Revimid (now renamed Revlimid). He had a horrible reaction to Revimid including rash, diarrhea, fatigue and he became incoherent. He was hospitalized for 3 days in August 2006 and when released he was told to take the Revlimid again. He completely stopped taking Poly-MVA despite his wife's urging him to do so. He did not regain his full brain function and also underwent some personality change and became short tempered. Shortly after he was hospitalized with the same symptoms and released 4 days later. He was given oral pain medications to manage his bone pain. He was later switched to a pain patch. He started to decline rapidly and received home hospice care and intravenous morphine. Early November 2006 he got up to go to the bathroom and fell and cracked his ribs. He died shortly thereafter on November 9, 2006. By following an integrative treatment plan he was able to exceed the 90-day lifespan that his oncologist predicted when he was first diagnosed in March 2001 with an excellent quality of life until shortly before his death.

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