A New Era in Treating Patients Who Have Multiple Myeloma

By Kate Newberry

During the past decade, several novel treatments have extended the median survival time for patients with multiple myeloma from less than 3 years to more than 7 years, and researchers are working to further improve treatment.

Multiple myeloma was first discovered more than a century ago, but until about 50 years ago there were no known treatments. Each year approximately 20,000 people in the United States are diagnosed with this blood cancer, and about 11,000 die of their disease. Patients with symptomatic disease develop fractures, severe bone pain, fatigue, infections, and hypercalcemia; if left untreated, these patients typically live less than 1 year.

Therapeutic agents

The first breakthrough in treating multiple myeloma came in the 1960s with the introduction of melphalan, an alkylating agent. Melphalan combined with prednisone increased the median survival time from less than 1 year to approximately 3 years. However, it was not until the 1980s that further progress was made when high-dose chemotherapy combined with autologous stem cell transplantation was introduced.

Two more decades passed before the next breakthrough in treating multiple myeloma; in 2003 bortezomib—the first of a new generation of therapies that inhibit proteosome
activity, thereby allowing cell death to occur in myeloma cells—was approved by the U.S. Food and Drug Administration (FDA) for the treatment of multiple myeloma.

Since that time, several therapies that target not only cancer cells but also the bone marrow microenvironment have been approved by the FDA for the treatment of multiple myeloma, and several more are being tested in preclinical and clinical studies. Other drugs approved between 2003 and 2008 for multiple myeloma treatment include thalidomide and lenalidomide, which are immunomodulatory agents with antiangiogenic effects; and liposome-encapsulated doxorubicin, which induces cell death by interfering with DNA replication. Although these drugs are effective individually, they have been shown to be much more effective when used in combinations. But despite the development of these more effective therapies, nearly 100% of patients eventually have disease relapse.

**“We are right in the middle of an era of new therapies.”**

– Dr. Michael Wang

“The current challenge is to find new drugs that treat relapsed disease and prolong survival,” said Michael Wang, M.D., director of the myeloma tissue bank and an associate professor in the Department of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center. “We are right in the middle of an era of new therapies,” Dr. Wang said. “We have prolonged median survival to about 7 years with new agents.”

**Current standard of care**

Multiple myeloma is thought to develop over several years and generally is treated only when a patient becomes symptomatic. The current standard of care is 2–3 months of induction therapy including novel drugs such as bortezomib, lenalidomide, and dexamethasone. Muzaffar Qazilbash, M.D., an associate professor in the Department of Stem Cell Transplantation and Cellular Therapy, said, “These days, more than 80% of patients respond to induction therapy. It used to be 50%–60% or even fewer when we didn’t have that many effective agents.” This is very important, as initial disease control is necessary before collecting the patient’s stem cells for transplantation.

After induction therapy, the patient’s stem cells are collected and banked, and 1–2 days of high-dose chemotherapy with intravenous melphalan is given to destroy any resistant cells. “High-dose chemotherapy eradi- cates the myeloma cells, but in the process it also wipes out the normal hematopoietic system and the immune system,” said Dr. Qazilbash. Thus, to replenish the blood and immune sys-

### CLINICAL TRIALS: Multiple Myeloma

The following clinical trials of treatments for multiple myeloma are currently enrolling patients at MD Anderson.

A trial of single autologous transplant with or without consolidation therapy versus tandem autologous transplant with lenalidomide maintenance for patients with multiple myeloma (BMTCTN0702). Principal Investigator (PI): Muzaffar Qazilbash, M.D. This phase III study compares three treatment arms in which patients receive an autologous stem cell transplant plus: lenalidomide, lenalidomide with a second autologous stem cell transplant, or lenalidomide with bortezomib.

A randomized, multicenter, phase III study comparing carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in subjects with relapsed multiple myeloma (2010-0416). PI: Michael Wang, M.D. The goal of this study is to learn if adding carfilzomib to the combination of lenalidomide and dexamethasone can help to control relapsed multiple myeloma.

An open-label, dose-escalation, phase I/II study of the oral form of MLN9708, a second-generation proteasome inhibitor, in adult patients with relapsed and refractory multiple myeloma (2009-0355). PI: Dr. Wang. The goals of this study are to learn the highest tolerable dose of MLN9708, to learn more about how MLN9708 works in the body, and to study the safety of the drug.

A phase I trial evaluating the safety and efficacy of vorinostat plus lenalidomide, bortezomib, and dexamethasone (RVD) for patients with newly diagnosed multiple myeloma (2008-0794). PI: Jatin Shah, M.D. The goal of this study is to find the highest tolerable dose of vorinostat that can be given in combination with RVD.

Randomized phase II trial of two stem cell doses to reduce transplantation-induced symptom burden in high-risk patients with multiple myeloma or amyloidosis (2005-060). PI: Nina Shah, M.D. The goal of this study is to learn whether higher doses of stem cells can help to decrease the symptoms that occur after melphalan treatment.

Phase I/II study of lenalidomide, thalidomide, and dexamethasone in patients with relapsed/refractory multiple myeloma (2009-0179). PI: Dr. Jatin Shah. The goals of this study are to find the highest tolerable dose of the combination of thalidomide, lenalidomide, and dexamethasone and to learn if the drug combination can help control the disease.
Improvements in Stem Cell Transplantation

Over the past 20 years, autologous stem cell transplantation has evolved and is now considered a relatively safe procedure. Although once offered only to younger patients, the procedure is now given to patients up to 80 years old. “Autologous stem cell transplantation is an intense procedure, but it is safe,” said Muzaffar Qazilbash, M.D., an associate professor in the Department of Stem Cell Transplantation and Cellular Therapy. “Our fatal complication rate has consistently been less than 2%. Almost all of our patients fully recover.”

Numerous factors have contributed to improvements in the safety and efficacy of autologous stem cell transplantation. Over the years, oncologists have learned more about the safety of the procedure. Better diagnostic tests have become available to detect infections, and these infections can be treated with better supportive care such as new antibiotics and antifungal treatments. In addition, new antiemetics and pain medications are available for managing the side effects of treatment.

Dr. Qazilbash also noted the importance of a team approach to stem cell transplantation. “Older patients may have a history of cardiac or pulmonary disease or renal failure,” he said. “But we have shown that even these patients can safely undergo transplantation as long as you identify these issues and have the patient evaluated by a cardiologist or nephrologist who treats these underlying conditions.”

As a testament to the safety of autologous stem cell transplantation, the majority of patients are treated as outpatients. Dr. Qazilbash said that the only reason for hospital admission would be the occurrence of complications such as fever, neutropenia, or nausea and dehydration.

The ultimate goal of therapy is to achieve complete remission, which until recently could be achieved only by stem cell transplantation. However, today combinations that include lenalidomide or bortezomib as frontline therapy are achieving durable complete remissions in some patients, enabling them to delay or even forgo stem cell transplantation. A combination of bortezomib, dexamethasone, and either thalidomide or lenalidomide appears to be emerging as the best initial treatment.

The treatment regimen given depends on whether a patient is eligible for a stem cell transplant. Most patients who are eligible eventually undergo autologous stem cell transplantation, either as part of their initial treatment regimen or after disease relapse.

A multicenter, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma (2010-0398). PI: Donna Weber, M.D. The main objective of this study is to compare progression-free survival in patients treated with panobinostat, bortezomib, and dexamethasone to that of patients treated with bortezomib and dexamethasone alone.

Phase I/II study of the combination of lenalidomide with high-dose melphalan for autologous transplant in patients with multiple myeloma (2008-0661). PI: Dr. Qazilbash. The goal of this study is to evaluate the safety of escalating doses of lenalidomide with high-dose melphalan in patients with relapsed multiple myeloma who will receive an autologous stem cell transplant.

Evaluation of lenalidomide as maintenance therapy post–allogeneic hematopoietic cell transplantation for high-risk multiple myeloma (2008-0329). PI: Dr. Qazilbash. The purpose of this study is to learn the feasibility of using lenalidomide as a follow-up treatment after an allogeneic stem cell transplant for multiple myeloma.

Randomized phase II trial of Id-specific donor vaccinated lymphocyte infusion for patients with myeloma relapsing or failing to achieve a complete remission after an allogeneic transplant (2004-0660). PI: Dr. Qazilbash. The goal of this study is to learn if vaccinating a donor with a patient’s purified myeloma protein and then injecting it back into the patient will result in a better response to allogeneic stem cell transplantation.

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esting research is being done as part of a Specialized Programs of Research Excellence grant for myeloma. Collaborators including Larry W. Kwak, M.D., Ph.D., chair of and a professor in the Department of Lymphoma and Myeloma at MD Anderson, and Carl June, M.D., at the University of Pennsylvania. These researchers are hoping to improve patients’ responses to chemotherapy by priming the immune system to selectively kill myeloma cells. The approach involves using a vaccine developed from patients’ own myeloma proteins combined with patients’ T lymphocytes.

According to Dr. Wang, potentially better chemotherapy drugs are in the pipeline. For example, carfilzomib, a second-generation proteasome inhibitor, is being tested in a phase II clinical trial at MD Anderson and other centers in patients with relapsed or refractory multiple myeloma who have received one to three prior therapies but not bortezomib.

Initial data from this trial presented at the 51st Annual Meeting of the American Society of Hematology showed that 45% of participants responded to carfilzomib. Furthermore, carfilzomib did not cause peripheral neuropathy, a dose-limiting toxicity of the older drugs thalidomide and bortezomib. “These findings are truly an advance for patients with multiple myeloma,” said Dr. Wang. “This is a challenging disease with devastating consequences. While new agents are extending life expectancies, they often have adverse side effects, including severe neuropathy. Carfilzomib is showing good response rates and an improved side effects profile.”

Carfilzomib is now being tested in combination with lenalidomide and dexamethasone in a phase III clinical trial at MD Anderson. Furthermore, the FDA has granted fast track designation for carfilzomib, which will allow for the accelerated approval of this drug for treating multiple myeloma.

Other new drugs for myeloma being tested in clinical trials at MD Anderson include panobinostat, a nonselective histone deacetylase inhibitor; ARRY-520, a kinesin spindle protein inhibitor; and KW-2478, a heat shock protein inhibitor. All of these drugs act to induce cell death through different mechanisms.

Although these studies are in the early stages, Dr. Wang predicted that genetic profiling will influence practice eventually. In fact, he said that gross genetic features have already changed treatments for some patients. For example, multiple myeloma patients whose tumor cells contain chromosome 13 monosomy, 17p deletion, or some chromosome 14 translocations are considered to have high-risk myeloma. For patients with these chromosomal abnormalities, a more aggressive course of treatment usually is recommended. However, more preclinical research and clinical trials will be necessary to determine whether certain treatments are better suited for patients whose tumors have certain genetic characteristics.

Thanks to the breakthroughs of the past decade, patients with multiple myeloma are living longer than ever with better quality of life. Furthermore, new treatments being tested preclinically and clinically—along with further analysis of the genetic profile of multiple myeloma—provide hope for even better outcomes in the future. “We are increasing the rate of complete remissions and prolonging survival,” Dr. Wang said. “But our ultimate goal is to one day cure multiple myeloma.”

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Dr. Michael Wang …………713-792-2860

Landmark Trial Shows Lung Screening Can Be Beneficial

The preliminary results of the National Lung Screening Trial (NLST) show that lung cancer screening can be beneficial to people at high risk for the disease. However, questions remain concerning who should be screened and how often.

Specifically, the NLST found that over the course of the study, low-dose helical computed tomography (CT) offered a lung cancer—specific mortality reduction of 20.3% and an all-cause mortality reduction of 6.9% compared with standard chest radiography in people considered to be at high risk for lung cancer. The clinical practice implications of these and other findings from the trial may not be known for some time, however.

Reginald Munden, M.D., a professor in the Department of Diagnostic Radiology at The University of Texas MD Anderson Cancer Center, was the study’s principal investigator at the institution.

“The trial provided a very rich repository of data, probably more data than we will ever be able to fully understand,” Dr. Munden said. “Even though we are in the very early phases of understanding lung cancer screening, this trial is still the most significant thing that’s ever happened in lung cancer because now we can detect a cancer early enough to cure somebody.”

Still, Dr. Munden said, “The trial may have raised more questions than it answered.”
Largest study of its kind

The NLST was a prospective randomized trial and the largest lung cancer screening trial to date, involving more than 30 institutions across the United States. When the NLST launched in 2002, it aimed to include 50,000 patients; more than 53,000 were enrolled within 18 months. Eligible participants were current or former smokers 55–74 years of age who had a smoking history of at least 30 pack-years and no history of lung cancer. (One pack-year is equivalent to 20 cigarettes smoked per day for a year.)

Participants were imaged at enrollment and annually for 2 years. Those in the study group underwent low-dose chest CT, while those in the control group underwent conventional chest radiography. In randomized trials, the control group typically gets the standard of care, but the standard of care in this case, Dr. Munden said, was to do no imaging. Chest radiography was performed in the control group because NLST researchers feared that not doing any imaging would cause some participants to drop out of the study. Although earlier trials had yielded no statistically significant data supporting the use of chest radiography for lung cancer screening, some researchers had interpreted those findings differently, saying that the benefit of screening with chest radiography, though small, was existent. Those researchers argued that radiographic screening of the control group could therefore obscure the true benefit of CT in the study group.

Even so, Dr. Munden said, “It’s probably better that we did chest radiographs in the control group because even if it has a benefit, we’ve far exceeded that with CT.”

Who should be screened?

The U.S. Food and Drug Administration has not approved CT for lung cancer screening. Although the NLST’s findings may change that, in the meantime, teams of researchers are scrambling to determine which populations are most likely to benefit from the screening protocol.

“It’s extremely important that we screen people who are truly at risk for lung cancer,” Dr. Munden said.

Yet opinions of what constitutes high risk can vary widely. Right now, the question of who should be screened—other than those meeting the criteria of the NLST—is open for interpretation.

For example, “We know that there’s a huge group of head and neck cancer survivors—long-term survivors—who smoke. They are at a much higher risk of developing lung cancer than a smoker who has never had head and neck cancer,” Dr. Munden said. “That kind of person is someone I’d consider at high risk and would probably screen,
but that’s not the kind of person we screened in the trial.”

Most researchers, Dr. Munden said, agree that individuals at high risk are those who have had heavy exposure to smoking and have lived long enough to develop lung cancer. Many researchers believe such a person is one who has a smoking history of 20 or more pack-years and is at least 50 years of age.

“Part of the issue is who not to screen as much as it is who to screen,” Dr. Munden said. “What we do not want to do is screen a 40-year-old woman who has a casual or minimal smoking history, because the benefit does not justify the risk.”

Chief among the screening procedure’s risks is ionizing radiation exposure, which can increase a patient’s lifetime risk of developing cancer. (The risk is higher in women because breast tissue, which is highly radiosensitive, also receives the most radiation from chest CT.) In the United States, the average annual exposure to ionizing radiation is about 3.1 mSv—half from natural sources and half from manmade sources, mostly diagnostic medical procedures. Diagnostic CT delivers up to 8 mSv. Low-dose CT, which was used in the NLST, delivers about 1.5 mSv. By comparison, a series of conventional chest radiographs delivers about 0.06 mSv. In older patients with a long history of smoking—such as those included in the NLST—the benefit of identifying a cancer at a treatable stage is more likely to outweigh the risk a small dose of ionizing radiation conveys.

In the absence of established screening guidelines, Dr. Munden said, physicians should rely on their experience and judgment in determining which patients are at high risk. “If you think a patient of yours has a significant risk of lung cancer based on some criteria that you’re comfortable with, I encourage you to get the patient screened,” he said.

**Biomarker studies**

In addition to undergoing CT or chest radiography, more than 10,000 trial participants—including those enrolled at MD Anderson—submitted sputum, blood, and urine specimens as part of the NLST’s biomarker study. The goal of the biomarker study is to identify genetic differences between trial participants who developed lung cancer and trial participants who did not develop lung cancer. Although it is not yet under way, according to Dr. Munden, the biomarker study is integral to identifying the best candidates for lung cancer screening.

“To me, this will be the most important part of the trial,” Dr. Munden said. “If you think about who should be screened for lung cancer, the answer’s probably in a blood test that tells us this person has the genetic predisposition to develop lung cancer. That’s the person we’ll screen.” However, Dr. Munden added, “We’re not anywhere close to being there.”

**Lung cancer screening at MD Anderson**

Dr. Munden and other faculty members—including Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention; Stephen Swisher, M.D., chair of and a professor in the Department of Thoracic and Cardiovascular Surgery; and George Eapen, M.D., an associate professor in the Department of Pulmonary Medicine—are in the initial phases of establishing a lung cancer screening program at MD Anderson.

“We’re not just going to screen people,” Dr. Munden said. “We want to collect data that can help answer some questions down the road, so the program will have a clinical research component as well.” He added that a smoking cessation program is offered as an integral part of the screening program.

The group has initiated the screening program at MD Anderson’s main campus in the Texas Medical Center and plans to eventually implement the program at the institution’s regional care centers. People aged 50 years and older with a smoking history of at least 20 pack-years are eligible. A physician referral is not required, Dr. Munden said, but patients must have a doctor who can be contacted in the event something is found. Physicians are encouraged to refer patients they believe to be at a high risk of developing lung cancer.

**More questions**

Dr. Munden said that the initial results of the NLST are expected to be published this summer. In the meantime—and for some time hereafter—NLST researchers will continue to grapple with the multitude of questions raised by the trial’s findings.

“The bigger questions now are, who do we screen and when do we screen them? And how often do we screen them?” Dr. Munden said. “As we discover answers to these and other questions, lung cancer screening programs will help us improve people’s health and save lives.”

FOR MORE INFORMATION
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**ADDITIONAL RESOURCES**


Eating Healthier May Reduce Cancer Risk

Healthy eating habits may also increase energy and heart health

You probably know that a diet rich in fruits and vegetables decreases your risk of heart disease, but you may not have heard that these foods might also decrease your risk of certain types of cancer.

Plant foods contain phytochemicals, which are chemical compounds that occur naturally in plants and may protect against cancer. Diet experts recommend that at least two-thirds of your plate be filled with vegetables, fruits, whole grains, and beans (including peas and lentils). Eating more of these foods may lower your risk of developing cancers at several sites, including the breast, digestive tract, lung, and prostate.

Increasing your daily intake of fruits, vegetables, and beans is easier than you might think. For example, you can:

• eat a variety of vegetables, particularly red, orange, and dark green vegetables, as well as beans and peas;
• carry a piece of fruit and a bag of bite-sized vegetables with you for a snack;
• grate vegetables, such as zucchini or carrots, into spaghetti sauce and casseroles; and
• eat one or two servings of fruits and vegetables at each meal and snack.

More fiber, less red meat

Dietary fiber is the part of fruits, vegetables, and grains that the body does not digest. According to the American Institute for Cancer Research, studies have shown that eating foods high in fiber may reduce your risk of colon cancer.

As you increase the amount of fruits, vegetables, and beans you eat each day, the amount of fiber in your daily diet will naturally increase, too. But you also need to replace refined grains (like white flour and white rice) with whole grains (like whole wheat flour and brown rice) to reach your daily fiber goals. Women should eat at least 25 grams of fiber each day, and men should eat at least 38 grams of fiber per day.

You can increase your intake of fiber by including the following:

• one medium-sized pear, apple, orange, or banana (3–5 grams of fiber);
• ½ cup of cooked black beans (6–9 grams of fiber);
• ¼ cup of bran cereal (5 grams of fiber); and
• one small baked potato with the skin (3 grams of fiber).

Eating large amounts of red meat (including beef, pork, lamb, and goat) and processed meat (which has been smoked, cured, salted, or treated with other preservatives) may increase your risk for colon cancer.

The American Institute for Cancer Research recommends a personal goal of eating no more than 18 ounces (500 grams) of red meat per week and consuming little, if any, processed meat.

Healthy habits

Changing your eating habits may take some time, but the benefits are worth the effort. In addition to decreasing your risk of heart disease and possibly cancer, a healthy diet will increase your physical energy and mental well-being. To make eating healthy a lifelong practice, try these strategies for adopting a new healthy habit:

Make smart goals. Take small steps that are measurable, attainable, realistic, and timed. For example, your goal for the first month might be to double your daily intake of fruits and vegetables.

Focus on rewards instead of punishment. Treat yourself to a reward, like a massage or a movie, when you reach a goal. Rather than punishing yourself when you slip up, remind yourself of the steps you have taken toward living a healthier lifestyle.

Go public. Let others know you have decided to change your eating habits. Your friends and family can provide encouragement.

Learn more about nutrition. Gather information from your health care provider, books, Web sites, and support groups.

Keep a food diary. Keeping track of what you eat will make you more aware of your behavior and more accountable for your choices.

Eating healthy will also help you maintain a healthy weight. Since obesity increases the risk for cancers of the colon, uterus, breast (after menopause), esophagus, pancreas, and kidney, maintaining a healthy weight may further decrease your risk of cancer.

– S. Moreau

FOR MORE INFORMATION
• Talk to your physician
• Visit www.mdanderson.org
• Call askMDAnderson at 877-632-6789
• Visit the American Institute for Cancer Research at http://www.aicr.org
• Visit the USDA Dietary Guidelines for Americans at http://www.dietaryguidelines.gov

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Inotuzumab Ozogamicin Shows Promise for Acute Lymphoblastic Leukemia Treatment

Promising results from a clinical trial of a new targeted therapy for acute lymphoblastic leukemia (ALL) were presented at the 2011 annual meeting of the American Society of Clinical Oncology by MD Anderson researchers.

In this ongoing trial led by Hagop Kantarjian, M.D., a professor in and chair of the Department of Leukemia, researchers tested the effectiveness of inotuzumab ozogamicin for treating therapy-resistant or refractory ALL. They found the drug to be surprisingly effective.

Of 46 patients evaluable for response, 9 had a complete response, 14 had a complete response without full recovery of platelets, and 5 had less than 5% blasts in their bone marrow without platelet recovery.

“A response rate of more than 50% in this patient population probably makes inotuzumab ozogamicin the most active single-agent therapy ever for ALL,” said Dr. Kantarjian. Many second-line treatment options for ALL offer response rates of only 20%–30%.

Inotuzumab ozogamicin is the first drug of its kind for the treatment of ALL. The drug is a combination of a monoclonal antibody that targets ALL cells and of calicheamicin, a powerful cytotoxic agent.

Because ALL arises from lymphoblasts, which are the bone marrow precursors to lymphocytes, most ALL cells express CD22, a marker of lymphocytic development. This molecule is the target of inotuzumab ozogamicin’s antibody component.

When inotuzumab ozogamicin binds to CD22, both calicheamicin and CD22 are taken up by ALL cells. Once inside a cell, calicheamicin, an antibiotic, readily cleaves the cell’s DNA to induce cell death. In this way, inotuzumab ozogamicin selectively kills the cancer cells while sparing most healthy cells.

In the study, most of the side effects of inotuzumab ozogamicin were mild or manageable; the most common side effect was fever. This safety profile and the high response rate make the drug promising for future trials. In fact, a phase II clinical trial that combines inotuzumab ozogamicin with rituximab, another antibody-based chemotherapy drug that targets leukemia cells, is already under way.

Future clinical trials may be needed to examine different dosing schedules for inotuzumab ozogamicin, which was given every 3 weeks in the initial study. The researchers suggested that weekly administration may increase the effectiveness of the drug.