

# OncoLog

MD ANDERSON'S REPORT TO PHYSICIANS ■ February 2011 Vol. 56, No. 2

## Surgeons Use Computer-Generated Models for Jaw Reconstruction

By Bryan Tutt

**Recent advances in technology have enabled surgeons to perform facial reconstruction with a degree of precision that was impossible just a few years ago.**

Resection of head and neck tumors can leave patients permanently disfigured, especially if sections of bone must be removed along with the tumor. Because cancers of the head and neck often involve the mandible or the maxilla, reconstructive surgeons are constantly seeking new techniques to rebuild patients' jaws to match the original as precisely as possible.

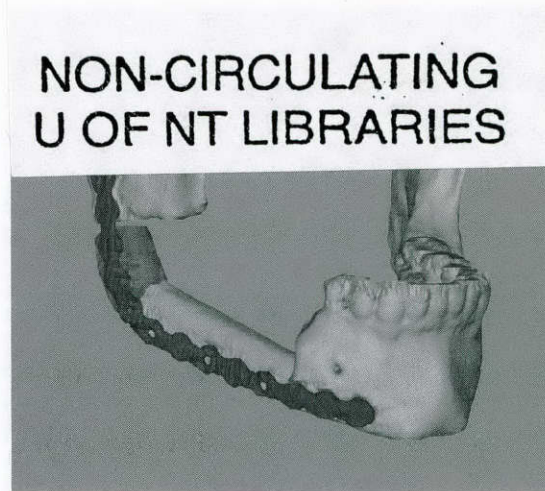
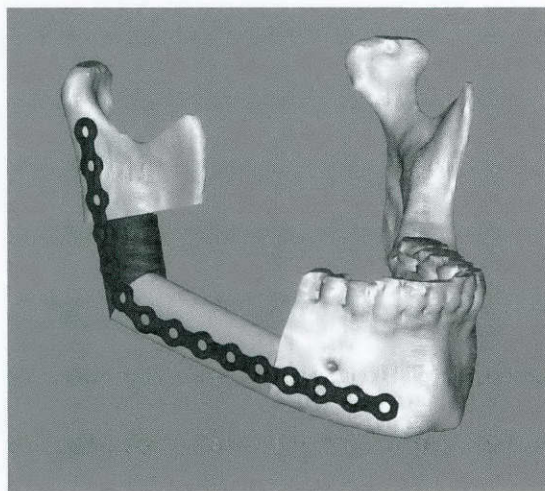
"Reconstructive surgery has come a long way in our lifetimes," said Matthew Hanasono, M.D., an associate professor in the Department of Plastic Surgery at The University of Texas MD Anderson Cancer Center, who explained that the current technique for jaw reconstruction using tissue harvested from the patient's leg was developed in the early 1980s. Since then, surgeons at MD Anderson and other institutions have worked

to refine the technique. These efforts have led to an unusual collaboration between surgeons and engineers to create virtual and physical models of patients' bones using software and tools adapted from the manufacturing industry.

### Reconstructing the jaw

When head and neck surgeons have to remove part of a patient's jaw bone to resect a tumor, the plastic surgeon's ability to rebuild the jaw to match its former shape affects not only appearance but also functions such as eating and speech. Chronic pain in the temporomandibular joint also can result from an imperfectly aligned jaw.

The standard reconstruction technique involves harvesting a section of the fibula and any necessary skin, muscle, or fat from the patient's leg. The surgeons cut the harvested



A virtual plan of a fibula flap reconstruction (left) was used to help surgeons rebuild a patient's mandible. A three-dimensional computed tomography image (right) obtained postoperatively shows the actual reconstruction.

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# Surgeons Use Computer-Generated Models for Jaw Reconstruction

[Continued from page 1]

section of bone into pieces, which are then formed together along a titanium plate, which the surgeons have bent to match the shape of the original mandible or maxilla as closely as possible. “This is where plastic surgery can become an art,” said Roman Skoracki, M.D., an associate professor in the Department of Plastic Surgery. Autologous tissue transplants, or free flap transfers, are used to rebuild the lining inside the mouth and/or the facial skin. All of this is done immediately following the tumor resection.

To complete the reconstruction, Dr. Skoracki said, “Our dental colleagues anchor osseointegrated implants to the new jaw bone. For all intents and purposes, these act like the patient’s natural teeth.”

Because the tibia is the main weight-bearing bone in the lower leg, the middle portion of the fibula can be removed without causing disability to the patient—Dr. Skoracki described the fibula as “a built-in spare part.” Patients who have jaw reconstruction using a fibula flap typically are able to resume walking within 5 days, eat solid food within 2 weeks, and resume normal activity within 3 months. However, recovery may take longer for patients receiving adjuvant chemotherapy or radiation therapy.

## Limitations of reconstructive surgery

One area of concern for surgeons performing jaw reconstruction is the amount of time required for the surgery. When patients undergo resection of a tumor from the mandible or maxilla followed by reconstruction with autologous tissue, they are under general anesthesia for 10–12 hours. Dr. Skoracki said, “Our part of the surgery—harvesting the leg bone, reconstructing the jaw to the shape we want it to be, finding the appropriate donor blood vessels to use, setting the plate and tissue into place, resurfacing the inside of the mouth where it may be necessary, attaching the blood vessels under the microscope, and finally putting the

external skin back together—takes 6–8 hours.”

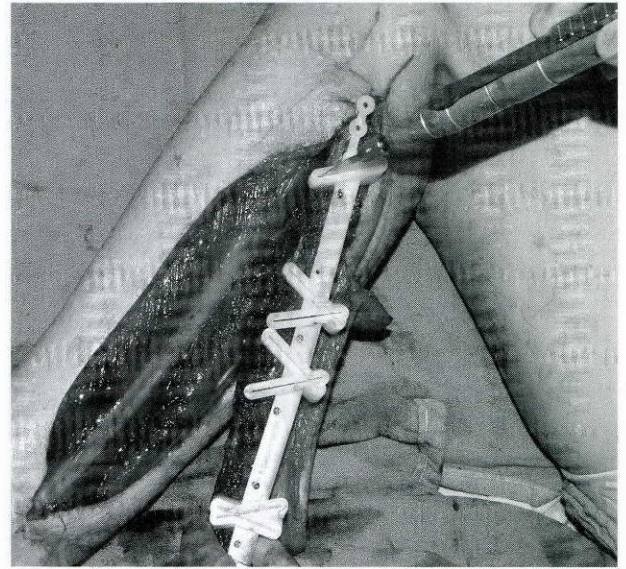
Dr. Hanasono said, “If we can cut that time by a couple of hours, it benefits the patient in many ways, including lowering blood loss and risk of infection.”

In standard autologous tissue reconstruction, the titanium plate must be measured and bent to match the patient’s existing jaw bone. But for some patients, this is not possible. “Some patients have very distorted bones—from the tumor itself, from previous surgery, or from osteonecrosis from radiotherapy,” Dr. Skoracki said. “The challenge in reconstructing a jaw for these patients is that you can’t place the plate on the original bone to bend it—the ‘normal’ is not there.”

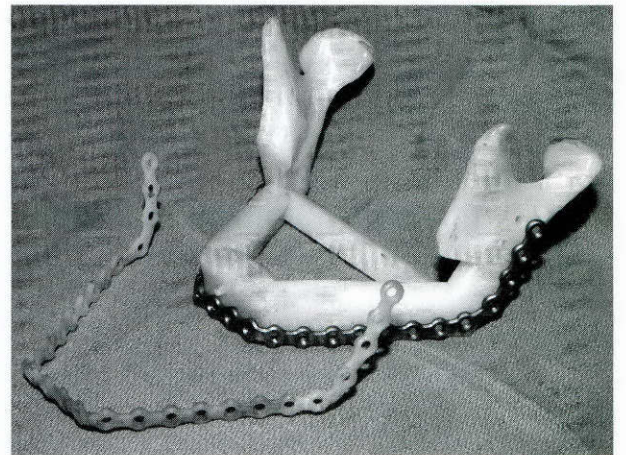
## Borrowed technology

The difficulty in estimating the shape of the plate—and the resulting pain and loss of function for patients whose rebuilt jaws did not align perfectly—led surgeons to search for a more precise technique.

“We worked with a software design company to develop a modified version of computer-assisted design software, which is used in drafting and engineering, specifically for the craniofacial skeleton,” Dr. Skoracki said. The software creates a virtual replica of the patient’s anatomy from magnetic resonance imaging (MRI) or computed tomography (CT) images of the patient’s jaw. The software helps surgeons to plan the reconstruction by creating the exact shape of the jaw that will be resected. The surgeons can then cut a virtual fibula to the exact angles that will



A surgeon uses a reciprocating saw to make osteotomies according to a plastic cutting guide placed on the patient’s fibula. The cutting guide was created from a virtual plan for a fibula flap jaw reconstruction.



A titanium plate for a fibula flap reconstruction is bent preoperatively to match plastic models of the patient’s mandible and of the plate itself.

optimize bone apposition, further helping plan the surgery.

To take this planning aid from the computer screen to the physical world, physicians at MD Anderson, working with another design company, developed plastic cutting guides that can be snapped in place on the fibula so that it can be cut to the exact lengths and angles defined by the virtual plan. These cutting guides are created using a three-dimensional printer—a technology used in the manufacturing industry to make prototypes—which prints the starch



or polymer model layer by layer. The printer can also produce a three-dimensional replica of a patient's jaw.

"It's wonderful to have these models because we have an exact template of what the ideal would be," Dr. Skoracki said. "We can bend plates on the model, which allows us to be more exact in our reconstruction. We can actually perform surgery on these acrylic or starch models to rehearse."

In addition to improving the accuracy of reconstruction, Dr. Hanasono said that the models reduce the time required for surgery because the surgeons can bend the titanium plate to the correct shape before surgery.

### Accessible technology

Surgeons at MD Anderson outsource the virtual modeling and three-dimensional printing to a private company. The surgeons send the patient's MRI or CT images to engineers at the company and discuss the case with them in videoconferences. The engineers then create the virtual models, and if needed, physical models and cutting guides are printed and shipped.

Because the private contractor can create these models from imaging studies, the technology is available to surgeons at almost any institution. Dr. Skoracki said the models can be especially beneficial to surgeons who perform only one or two jaw reconstructions per year. "This technology helps the surgeon plan the surgery and execute it more precisely," he said.

Dr. Hanasono said that surgeons at MD Anderson do more jaw reconstructions using autologous tissues than any hospital in the United States, but the models are used only for the most complicated cases—about 12 per year.

Dr. Skoracki added, "We use the whole gamut of these technologies for those patients who have very large tumors that prevent us from doing the measurements necessary for the usual method of reconstruction."

Dr. Hanasono pointed out that the full potential of the modeling technology has not yet been realized. "This tech-

## Body Image Therapy

**M**any cancer patients—especially those with tumors of the head and neck—face the possibility of disfigurement and functional difficulties stemming from the disease as well as its treatments.

One source of help for these patients is MD Anderson's Body Image Therapy Program, which provides psychosocial services to patients before and after reconstructive surgery. The program, led by Michelle Cororve Fingeret, Ph.D., an assistant professor in the Department of Behavioral Science with joint appointments in the Departments of Head and Neck Surgery and Plastic Surgery, was launched in 2008.

"Our plastic surgeons can do amazing things, but there are bounds of reality that we have to work within," Dr. Fingeret said. Many of her patients have disabilities related to cancer or cancer treatment that make it difficult to speak or eat. While other therapists help these patients with functional rehabilitation, Dr. Fingeret helps them gain the confidence to go out in public and do the activities they used to enjoy doing.

"The basis of this program is to try to normalize and validate patients' body image concerns," she said. "Patients often feel that they are the only one experiencing these things. To have somebody come in and tell them they are not alone—that in itself really helps them feel more supported and encouraged to get back to living their lives."

Dr. Fingeret works as part of the multidisciplinary treatment team in the Head and Neck Center, where she counsels patients regardless of whether they are having reconstructive treatment. She helps some patients deal with anxiety before or during reconstructive procedures—some of which require multiple surgeries over several months—and helps others cope with their situation after the completion of their cancer treatment and reconstructive surgery. "When the plastic surgeons tell patients that no further improvement is possible—that's sometimes when the body image issues develop for patients who have been holding out hope that things would get better," she said.

Most of the program's patients are referred by the Center for Reconstructive Surgery; about half are being treated for head or neck cancer and half for breast cancer.

It is not uncommon for patients who have had surgery for breast cancer, even though the absence of a breast is usually not visible when the patient is dressed, to face the same issues of social isolation or anxiety about body image experienced by survivors of head and neck cancer. "There are things we can do to target the way patients are thinking about things," Dr. Fingeret said, "but we'll also get them to increase the number of activities they participate in—things they find pleasurable."

Dr. Fingeret is also doing research to determine the nature and extent of the concern patients have about body image. "We expect all of our patients, to some degree, to have body image concerns," she said. "Body image concerns are normal." ■

nology has been in development for 8–10 years, but its current form has only been in use about 3 years," he said. "The technology has implications not only for cancer but for all types of reconstruction, including reconstruction in trauma patients." ■

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# Addressing Cancer-Related Health Disparities

Research aims to find causes and solutions

By Zach Bohannon

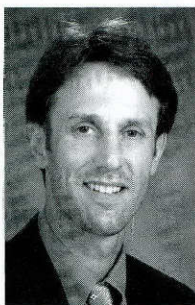
**Many people know that risk factors like smoking can cause cancer, but few can explain why cancer incidence and mortality rates vary among ethnic minority and underserved populations.**

Understanding these variations and developing targeted policies and interventions to reduce disparities are two of the main goals of health disparities research.

Once people are aware that different ethnic populations have different cancer rates, the first cause that comes to mind is genetics. However, “our best estimation is that biology accounts for only 10%–20% of cancer-related health disparities,” said David Wetter, Ph.D., the chair of the Department of Health Disparities Research at The University of Texas MD Anderson Cancer Center.

Consequently, the growing field of health disparities research includes a focus on potential risk factors, such as behavior and socioeconomic status.

The breadth of this subject makes the research very diverse, although much of the research—especially that involving cancer—is focused on the effects of lifestyle alteration and outreach programs. “Although there is a genetic component to health disparities,” Dr. Wetter said, “the far more relevant factor is societal influence.”

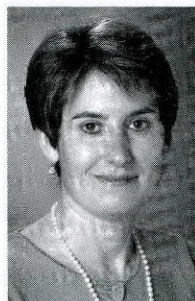


David Wetter,  
Ph.D.

## Health disparities research

Often, the first step to understanding health disparities is to quantify their effects. For example, Melissa Bondy, Ph.D., a professor in the Department of Epidemiology, recently published a report on the incidence of breast cancer in Mexican-American women. She and her colleagues found that although Mexican-American women experience a lower overall incidence rate of breast cancer, the breast cancers they do have are much more likely to be early-onset breast cancer than those in other portions of the population. However, the latest U.S. Preventive Services Task Force guidelines for breast cancer screening recommended increasing the initial mammography age from 40 to 50 years. These recommendations may be appropriate for a general population, but when universally recommended, they may miss early-onset breast cancers in Hispanic women.

Although this early onset of breast cancer may have a genetic component,

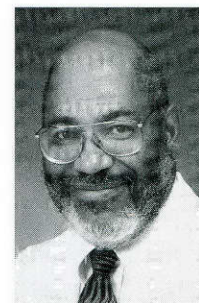


Melissa Bondy,  
Ph.D.

**“Our best estimation is that biology accounts for only 10%–20% of cancer-related health disparities. The far more relevant factor is societal influence.”**

– David Wetter, Ph.D.

health disparities researchers are careful to distinguish between biology and race. As Lovell Jones, Ph.D., the director of the Center for Research on Minority Health and a professor in the Department of Molecular Biology and Biochemistry and the Department of Health Disparities Research, said, “Race is a social construct and has little to no meaning genetically.”



Lovell Jones,  
Ph.D.

## Taking research to the community

Besides biology, health disparities research also encompasses a variety of community and cultural research. One of the goals of the Center for Research on Minority Health is to help integrate these diverse studies. The center supports a wide range of programs designed to investigate and enhance minority health. Many of these programs are outreach-oriented. For instance, the center is currently administering a program to explore the genetic and cultural similarities and differences between African American communities and West African communities in an attempt to research the genetic causes of breast cancer and educate women about breast cancer’s risk factors and warning signs.

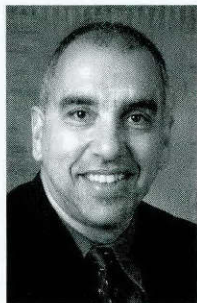
Dr. Wetter’s research also is aimed at designing, evaluating, and disseminating behavioral interventions. For example, some of his current studies focus on improving the effectiveness and reach of smoking-cessation help lines (quitlines) among underserved populations such as Hispanic smokers and smokers of low socioeconomic status. Quitlines provide behavioral counseling and, in many cases, pharma-



cotherapy. Unfortunately, quitlines are grossly underutilized by underserved populations. Research partnerships with organizations such as the Harris County Hospital District seek to dramatically expand quitline utilization among the underserved.

### Dispelling misconceptions

Another key area for concern among health disparities researchers is the prevalence of false or misleading beliefs among some populations about the nature of cancer and cancer treatment. Such beliefs can often persist despite contradictory evidence. Unfortunately, false beliefs lead many underserved populations to select substandard treatment options or to avoid treatment entirely. Furthermore, many individuals are reluctant to participate in clinical trials for historical reasons associated with unethical human experimentation. Fortunately, the trend of reluctance may be reversing, according to Harry



Harry Gibbs,  
M.D.

Gibbs, M.D., the Chief Diversity Officer at MD Anderson. For example, a series of focus groups revealed that although older African Americans are reluctant to participate in clinical trials because of the infamous Tuskegee Syphilis Study, younger African Americans do not share the same reluctance.

These types of focus groups help health professionals understand the cultural beliefs of patients and study participants from all walks of life. And when these beliefs are understood, researchers can develop targeted programs to enhance patient recruitment for clinical trials.

A clear example of effective targeted recruiting is MD Anderson's Minority and Women Clinical Trials Recruitment Program, which assists researchers in designing programs to increase the appeal of clinical trials to a broad cultural spectrum and then attempts to retain underserved populations in those trials. Dr. Wetter said, "Once they arrive at MD Anderson, underserved individuals show similar rates of parti-

cipation in clinical trials relative to other populations."

### Breaking through barriers

Although clinical trials don't always mean more successful treatment, they do often foster communication between patients and doctors or nurses. For instance, Dr. Jones described a clinical trial in which a diabetic patient from an underserved community insisted he was controlling his blood sugar even though his doctors believed he was noncompliant. After some investigation, the doctors and researchers realized that the patient didn't have a refrigerator, so he had been given insulin and was injecting it, but without refrigeration, its effectiveness decreased to zero in a few days. "Doctors don't have any government authority to ensure compliance," Dr. Gibbs said. "We have to build trust with our patients."

Another common barrier to the treatment of underserved populations is cultural differences between patients and health care providers. Dr. Gibbs em-

phasized the importance of cultural understanding, especially when end-of-life issues may arise. One of the many successful programs Dr. Gibbs has overseen is a nursing workshop devoted to these issues. Health disparities research can enable health care professionals to understand and accommodate the various beliefs about end-of-life and other treatment-related issues that may be encountered in a comprehensive cancer center.

Ultimately, the goal of health disparities research at MD Anderson is to eliminate avoidable differences in cancer incidence, morbidity, and mortality among various population groups, whether those groups are defined by socioeconomic status, race, ethnicity, gender, location, or other factors. ■

## Health Disparities Research Projects at MD Anderson

**Ask-Advise-Connect.** Principal Investigator (PI): Dr. Jennifer Irvin Vidrine. The goal of this study is to increase dissemination and enhance utilization of the State of Texas Quitline among a critically underserved and ethnically diverse population of smokers with very limited access to resources for quitting smoking.

**EXPORT Project, Bridging the Gap: Addressing Environmental Health Through Science.** PIs: Drs. Lovell Jones, Maria Hernandez-Valero, Richard Hajek, Janice Chilton, Beverly Gor, Gloria Regisford, George Stancel, Robin Fuchs-Young. This P60 grant from the National Institutes of Health (NIH) established the Center for Research on Minority Health as a center of excellence for community outreach research on health disparities. Components of the grant include support for long-term, multidisciplinary programs of research, education, and outreach in critical health problem areas in Houston and South Texas.

**African American Cancer Prevention Project Establishing a Cohort to Investigate Health Disparities (Project CHURCH).** PI: Dr. Lorna Haughton McNeill. The goal of this prospective cohort study is to examine the role of lifestyle/behavioral, social, and environmental factors on minority health and cancer-related disparities among a church-based sample of African-Americans in Houston.

**Community Networks Program Center.** PI: Dr. David Wetter. This new NIH-funded center addressing cancer disparities among Hispanics in Texas was formed in partnership with The University of Texas School of Public Health. ■

For more information about these and other studies and programs in MD Anderson's Department of Health Disparities Research, please call 713-563-8768 or visit [www.mdanderson.org](http://www.mdanderson.org).



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## Drug Combination May Benefit Acute Myelogenous Leukemia or Myelodysplastic Syndrome Patients Who Have Poor Prognosis

Patients with newly diagnosed acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who have poor performance status or a concurrent disease may benefit from combination treatment with azacitidine and vorinostat, according to early results of an ongoing trial.

At the 52nd Annual Meeting of the American Society of Hematology in December, Guillermo Garcia-Manero, M.D., a professor in the Department of Leukemia at MD Anderson, and his colleagues reported the early results of a phase II clinical trial, which is open only to AML and MDS patients with concurrent diseases or with Eastern Cooperative Oncology Group (ECOG) performance status higher than 2. ECOG criteria score patients' performance status from 0 (fully active) to 4 (completely disabled).

Dr. Garcia-Manero said that newly diagnosed patients with AML or MDS who have a poor ECOG performance status or an additional disease typically survive fewer than 60 days without treatment. However, these patients do not meet the eligibility requirements for most clinical trials and therefore often do not have access to experimental treatments that might prolong survival.

The purpose of the trial was to assess whether AML and MDS patients with concurrent diseases or poor ECOG performance status would benefit from the drug combination of azacitidine and vorinostat, which is known to be safe and active against AML and MDS in patients without such complications.

At a median follow-up of 3.6 months, 20 of 24 patients evaluable for survival had survived past 60 days.

Complete remissions (less than 5% blasts in the bone marrow, absolute neutrophil count over 1,000/ $\mu$ L, platelet count over 100,000/ $\mu$ L) were reported for 7 of the 15 patients who could be evaluated for response to the therapy.

"Our findings suggest current eligibility standards that prevent participation by these patients in phase I and phase II clinical trials might be inadequate," Dr. Garcia-Manero said. ■

## New Targeted Therapy for Hodgkin Lymphoma Shows Promise

In a phase I clinical trial, 38% of patients with relapsed or therapy-resistant lymphoma experienced complete or partial remissions when treated with the antibody-drug conjugate brentuximab vedotin.

"That level of objective response to a drug is impressive for a phase I trial," said Anas Younes, M.D., a professor and director of clinical and translational research in the Department of Lymphoma/Myeloma at MD Anderson and lead author of the study's report, which was recently published in the *New England Journal of Medicine*. "These encouraging results are being confirmed in a large phase II trial."

Of the 45 patients enrolled in the phase I trial, 42 had Hodgkin lymphoma, 2 had anaplastic large-cell lymphoma, and 1 had angioimmunoblastic T cell lymphoma. The patients had undergone a median of three previous chemotherapy regimens, and 73% of the patients had received autologous stem cell transplants.

Seventeen patients—15 with Hodgkin lymphoma and 2 with anaplastic large-cell lymphoma—had an objective response to treatment. Eleven responders had complete remissions, defined as disappearance of all evidence of the disease. The other 6 responders had partial remissions,

**"The potential impact of brentuximab vedotin on years of life saved is huge."**

— Dr. Anas Younes

defined as a 50% or greater reduction in the cumulative diameters of known malignant lesions and no new lesions.

The drug was given intravenously every 3 weeks, and the maximum tolerated dose was shown to be 1.8 mg/kg of body weight. Side effects at that dose were typically grade 1 or 2 in severity and included fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.

Brentuximab vedotin consists of cAC10—a monoclonal antibody that targets the CD30 cell surface protein—and monomethyl auristatin E, an inhibitor of tubulin proteins crucial to the formation of microtubules, which provide structure to cells and are necessary for cell division. CD30 is expressed on Hodgkin lymphoma and anaplastic large-cell lymphoma cells but is normally expressed on only about 1% of T cells and other immune system components; therefore, brentuximab vedotin selectively targets the lymphoma cells.

A unique aspect of Hodgkin lymphoma is that cancer cells make up only about 5% of the tumor while the rest of the tumor is composed of a variety of inflamed cells. "This is the first scientific evidence that if you eliminate a few cancer cells, the entire tumor can be degraded. Eliminate the 5% and the rest goes away," Dr. Younes said.

"There hasn't been a new drug considered for Hodgkin lymphoma in 30 years," Dr. Younes added. "The potential impact of brentuximab vedotin on years of life saved is huge because the median age for patients with this disease is in the 30s." ■

[See page 8 for more **IN BRIEF**]



# Traveling for Medical Treatment

## Advice from current and former patients and caregivers



### Traveling to another city for medical treatment brings a host of complications in an already stressful time.

The following tips on how to reduce the stress of the experience come from the experts: cancer survivors in the Anderson Network, MD Anderson's patient support program.

Receiving medical treatment far from home is challenging. Some of the biggest problems for network members were finding affordable places to live, dealing with transportation and scheduling issues, and figuring out how to feel comfortable in an unfamiliar city.

#### Ask for help

"My advice is to take advantage of the offers for help that friends and family make," a network member wrote. "Often their offers are nonspecific. Go ahead and tell them if you need a ride or need them to watch your children or pets. Stop worrying that you are asking for too large a favor. I found people were delighted and relieved to be asked to do something specific."

One cancer survivor asked her employer for help when the air and hotel costs started piling up. "They ended up buying all of my flights," she said. Another reported that when told no frequent-flyer seats were available, she explained to an airline agent that she was traveling for a medical appointment. After consulting with a supervisor, the agent found her a seat. "The lesson here is that the system often has room for exceptions, and people generally do want to help when possible," she wrote. "Feel free to explain why you need what you're asking for."

#### Search for discounts

Network members were resourceful in finding ways to cut costs.

Several people mentioned that some airlines offer medical discounts if patients ask for them, and various



nonprofit organizations offer travel grants. One member suggested that patients look for an Angel Flight program in their area; this service uses private planes with volunteer pilots to provide transportation to patients.

There were many suggestions on how to find housing. One member asked for—and received—special medical rates at motels near the hospital. Others found discount hotel rates through the Internet or used hotel frequent-stay points to book a room. Church-sponsored housing provided several with comfortable and inexpensive apartments. Network members advised finding housing near the hospital or staying in a hotel with courtesy vans for transportation to and from the hospital. Another cost-cutting tip was getting a hotel room with a kitchenette.

One member said he "networked with coworkers, friends, and church members until I found someone who knew a family in Houston, with whom I stayed. Besides reducing the costs, there was the added benefit of the supportive relationship and homey atmosphere."

#### Plan ahead

Advance planning could mean requesting a wheelchair at the airport, getting assistance boarding a plane, or bringing medication on the airplane in case of illness. One network member

said her doctor provided a packet with antibiotics and nausea medication for her to have when traveling. Another reported that having the prescriptions from her oncologist helped her to get through airport security with the containers of liquids she carried onboard.

Some members always kept their computed tomography scans and paperwork with them when traveling to protect the documents from loss or damage. Another anticipated long waits by always having a couple of good books and her MP3 player on hand.

Many survivors reported difficulty juggling multiple medical appointments and airline schedules. One member advised patients to never schedule a flight within 4 hours of an appointment.

#### Act like a tourist

Network members recommended seeing the sights of the destination city, such as museums and zoos, and taking scenic drives and walks through the park. One cancer survivor said she and her husband pretend they are on a vacation when traveling for medical care. Another wrote, "I traveled back and forth in a camper. It was fun."

#### Keep a positive attitude

One network volunteer summed it up this way: "There is really no challenge too big when you want to get effective treatment and control the disease. The biggest barrier when traveling out of town is yourself and your attitude, and you just have to make it work. It's worth it." ■

—K. Stuyck

#### FOR MORE INFORMATION

The Anderson Network is MD Anderson's support group of more than 1,700 current and former cancer patients. Their patient and caregiver support line is 800-345-6324.



## IN BRIEF

### Drug Shows Promise Against Treatment-Resistant Chronic Myelogenous Leukemia

Results of a clinical study indicate that the experimental drug ponatinib appears to be effective against treatment-resistant chronic myelogenous leukemia (CML).

Jorge Cortes, M.D., a professor in the Department of Leukemia at MD Anderson, presented these findings at the 52nd Annual Meeting of the American Society of Hematology in December.

CML is caused by the Philadelphia chromosome abnormality, a translocation between chromosomes 9 and 22 that results in the aberrant *BCR-ABL* gene. The first-line CML treatment imatinib and the second-line treatments nilotinib and dasatinib inhibit tyrosine kinases, a group of enzymes that play a variety of roles in controlling cell growth and differentiation. Although all three drugs inhibit the *BCR-ABL* protein, none of these drugs is effective against *BCR-ABL* proteins with the T315I mutation.

In the phase I clinical trial, the tyrosine kinase inhibitor ponatinib produced hematological and cytogenetic responses in patients whose leukemia cells carried the T315I mutation. The trial was open to patients whose disease had not responded to two or more prior treatments with imatinib, dasatinib, or nilotinib or had developed a resistance to at least two of these drugs.

“Ponatinib seems to be filling the gap

we had for patients who right now have no good treatments left,” Dr. Cortes said.

Fifty-seven of the 67 patients enrolled at the time of reporting had CML (42 in the chronic phase, 7 in the accelerated phase, and 8 in the blast phase). Three patients had Philadelphia chromosome-positive acute lymphoblastic leukemia, three had acute myelogenous leukemia, and four had other hematological malignancies.

Of the 42 patients with chronic phase CML, 32 were evaluable at the time of reporting. Thirty (90%) of these patients experienced a complete hematological response (normalization of the blood cell counts), and 12 (38%) had complete cytogenetic responses (absence of cells with the Philadelphia chromosome in the bone marrow). All 11 patients with chronic phase CML and the T315I mutation had complete hematological responses; eight of these patients also had complete cytogenetic responses.

The most common adverse events were thrombocytopenia, headache, nausea, arthralgia, fatigue, anemia, increased lipase, muscle spasms, rash, myalgia, and pancreatitis. All dose-limiting toxicities were reversible.

Dr. Cortes said patient enrollment has begun at MD Anderson and other institutions for a pivotal phase II trial of ponatinib in patients with treatment-resistant CML. ■

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