

New Agents Hold Promise for Patients With Advanced Thyroid Cancer

By Jill Delsigne

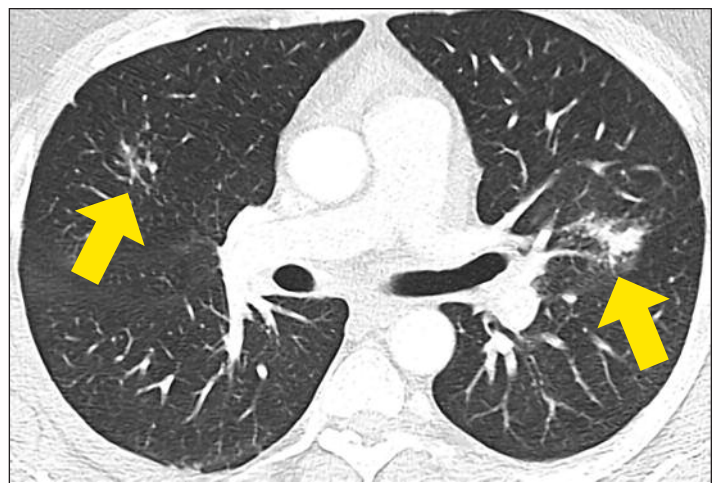
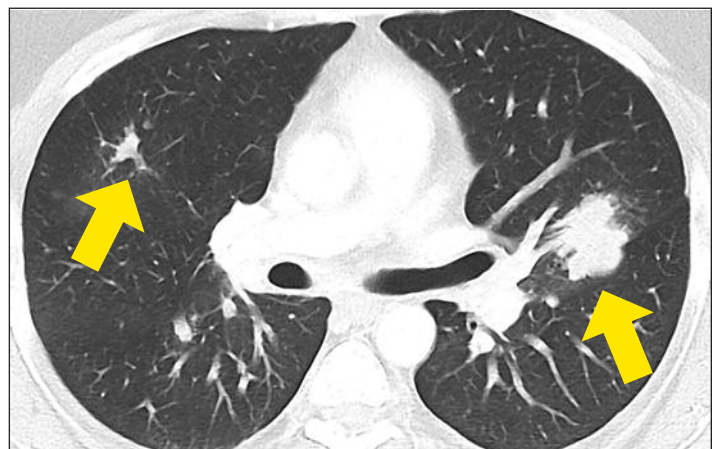
New agents are expanding treatment options for patients with advanced thyroid cancer—not only the papillary variant but also the less common medullary and differentiated variants of the disease.

“The new drugs provide hope for patients with metastatic thyroid cancer,” said Mouhammed Amir Habra, M.D., an assistant professor in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center. “Until recently, there were few options besides surgery and radioiodine treatment, which has limited efficacy. Now, we have promising and more efficacious treatment that is reasonably tolerated for patients with advanced disease.”

Metastatic disease is seen in a minority of thyroid cancer patients but constitutes a large proportion of cases at MD Anderson because of referral patterns.

Standard therapy

Partial or total thyroidectomy remains the first treatment option for metastatic thyroid cancer. Surgery is sometimes followed by radioiodine therapy, which has been used since the 1940s and was the first reported treatment to cure any type of metastatic cancer. However, because thyroid cancer cells often lose their ability to absorb iodine, radioiodine therapy has limited effectiveness against most cases of meta-



Computed tomography scans taken before (top) and after (bottom) 4 months of therapy with a tyrosine kinase inhibitor show the shrinking of lung metastases (arrows) from thyroid cancer.

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New Agents for Advanced Thyroid Cancer

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static thyroid cancer.

Other treatment options for metastatic thyroid cancer were limited until recently. Maria Cabanillas, M.D., an associate professor in the Department of Endocrine Neoplasia and Hormonal Disorders, said, “Cytotoxic chemotherapy is rarely effective in thyroid cancer, so 10 years ago we had little to offer patients with metastatic disease. There also were no effective targeted therapies for patients with advanced, progressive medullary thyroid cancer or radioiodine-refractory differentiated thyroid cancer.”

Dr. Habra recalled how helpless he felt when, as an endocrinology fellow at MD Anderson in 2002, he treated a thyroid cancer patient who had lung metastases: “The tumors did not respond to treatment, and he eventually died.”

Toward better therapy

The rarity of metastatic thyroid cancer has hampered the development of more effective therapy. Steven Sherman, M.D., a professor in and chair of the Department of Endocrine Neoplasia and Hormonal Disorders, explained that 10 years ago, pharmaceutical companies were resistant to drug development for thyroid cancer.

To overcome this challenge, Dr. Sherman said, “We made a strategic decision on how to engage the pharmaceutical industry in thyroid cancer research. If we could intelligently select a drug based on molecular abnormalities in the tumor and get early evidence of response to a drug, we felt we could leverage with a pharmaceutical company to advance it.”

This strategy led to the first successful international phase II trial of a targeted therapy for metastatic thyroid cancer. The study found motesanib, a vascular endothelial growth factor (VEGF) inhibitor, to be effective against progressive differentiated thyroid cancer. This success led to clinical trials of other agents for advanced thyroid cancer. “We now have two approved drugs, cabozantinib and vandetanib, for medullary thyroid cancer

“The new drugs provide hope for patients with metastatic thyroid cancer.”

– Dr. Mouhammed A. Habra

and one, sorafenib, for differentiated thyroid cancer,” Dr. Cabanillas said.

With these new agents, Dr. Habra said, “We can treat some thyroid cancers as chronic conditions that can be managed long-term. These patients used to go to hospice because we had no other treatment options. Not anymore.”

Recent research in the molecular pathogenesis of thyroid cancer has revealed several new pathways for targeted therapy. Dr. Sherman said, “As in many other forms of cancer, we are now identifying critical driver oncogenes that are important in the development of thyroid cancer. The MAP kinase pathway turns out to be particularly critical for both differentiated as well as medullary thyroid cancer. Eighty to ninety percent of patients with papillary thyroid cancer, the most common histology, will have an oncogenic mutation in *BRAF*, *RAS*, or *RET*. With the newest findings from studies like The Cancer Genome Atlas, we can also find less common mutations that might permit targeted therapy, like mutations in *ALK*.”

One of the most promising new

“[W]e are now identifying critical driver oncogenes that are important in the development of thyroid cancer.”

– Dr. Steven Sherman

agents for advanced thyroid cancer is lenvatinib (also called E7080). Lenvatinib selectively inhibits several tyrosine kinases that contribute to angiogenesis and cancer proliferation, including VEGF 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor- β , KIT, and RET.

Drs. Cabanillas and Habra were the local co-principal investigators on lenvatinib’s phase III trial, which enrolled nearly 400 patients with radioiodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression. More than 100 sites throughout Europe, Asia, and North and South America participated in the trial.

The results of the phase III trial were presented at the American Society of Clinical Oncology’s annual conference at the beginning of June. Patients treated with lenvatinib—even those whose disease previously did not respond to anti-VEGF therapies—had a significantly longer median progression-free survival duration (18.3 months) than placebo-treated patients did (3.6 months). Several patients treated with lenvatinib experienced a complete response to therapy. The drug’s most common side effects were hypertension, diarrhea, decreased appetite, weight loss, and nausea. Dr. Habra said the U.S. Food and Drug Administration is likely to approve the drug for differentiated thyroid cancer by the end of this year.

Other clinical trials are investigating drugs that target the *BRAF* protein kinase in papillary thyroid cancer. According to the American Thyroid Association, the V600E *BRAF* point mutation occurs in approximately 50% of papillary thyroid cancers and is associated with lymph node metastasis, distant metastasis, disease recurrence, and loss of radioiodine avidity, making the mutation a promising therapeutic target.

One such clinical study, led by Dr. Cabanillas, is investigating the effects of the *BRAF* inhibitor vemurafenib in patients with metastatic papillary thyroid cancer. According to the trial’s

preliminary report, 9 of the 26 treatment-naïve patients in the study had a confirmed partial response to the therapy (a more than 30% reduction in tumor size). These results were presented at the 2013 European Cancer Congress.

Unfortunately, papillary thyroid cancer can become resistant to BRAF inhibitors, resulting in only a partial response to therapy. Another research group at MD Anderson is investigating the mechanism of this drug resistance. The group is led by Marie-Claude Hofmann, Ph.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders. The group's preclinical research focuses on the role that estrogen receptors play in drug resistance to BRAF inhibitors, and the findings may also explain why papillary thyroid cancer occurs predominantly in women.

Looking forward

Despite the advances made so far, more progress is needed. According to Dr. Cabanillas, "We need to focus on salvage therapy, mechanisms of resistance, and finding a cure."

Fortunately, Dr. Habra said, "We are starting to understand the molecular pathways and genetics of thyroid cancer. We can pinpoint treatments that

are based on molecular markers, not just pathologic results, to choose the best treatment for each individual patient." ■

Thyroid Cancer Facts and Figures

The number of patients diagnosed with thyroid cancer has been rising in recent years, perhaps because advances in imaging modalities (particularly ultrasonography) facilitate earlier detection of the disease.

The American Cancer Society estimates that nearly 63,000 patients will be newly diagnosed with thyroid cancer in 2014. Of these new patients, the vast majority—more than 47,000—will be women. Nearly 1,900 people will die of the disease.

The most common types of thyroid cancer are papillary carcinoma, which accounts for 80% of cases, and follicular carcinoma, which accounts for 10% of cases. Fortunately, these types of thyroid cancer usually grow very slowly. Medullary thyroid carcinoma accounts for approximately 4% of thyroid cancer cases. This type of cancer can spread to other tissues before a thyroid nodule is even detected. However, medullary thyroid carcinoma can often be detected early by blood tests for calcitonin and carcinoembryonic antigen. The most aggressive form of thyroid cancer, anaplastic carcinoma, constitutes only 2% of thyroid cancer cases. ■

FOR MORE INFORMATION

Dr. Maria Cabanillas713-792-2841

Dr. Mouhammed Amir Habra ...713-792-2841

Dr. Steven Sherman713-792-2841

CLINICAL TRIALS: Thyroid Cancer

Phase II study of cabozantinib in patients with radioiodine-refractory differentiated thyroid cancer who progressed on first-line VEGFR-targeted therapy (2013-0220).

Principal investigator (PI): Dr. Maria Cabanillas. The main goal of this study is to learn if cabozantinib can help to control differentiated thyroid cancer. The safety of the drug will also be studied.

A randomized phase II study of concurrent intensity-modulated radiation therapy, paclitaxel, and pazopanib (NSC 737754)/placebo for the treatment of anaplastic thyroid cancer (RTOG0912).

PI: Dr. Gary Gunn. The goal of this study is to learn if the addition of pazopanib to paclitaxel and radiation is safe and tolerable.

A randomized phase II study of single agent GSK2118436 (dabrafenib) vs. combination regimen GSK2118436 and GSK1120212 (trametinib) in patients with BRAF-mutated thyroid carcinoma (2012-0349).

PI: Dr. Naifa Busaidy. The goal of this study is to learn if dabrafenib or the combination of dabrafenib and trametinib can help to control BRAF-mutated thyroid cancer. The safety of these drugs will also be studied.

A phase II, open-label study in subjects with BRAFV600E-mutated rare cancers with several histologies to investigate the clinical efficacy and safety of the combination therapy of dabrafenib and trametinib (2013-0918).

PI: Dr. Ralph Zinner. The goal of this clinical research study is to learn if the combination of dabrafenib and trametinib can help to control disease in patients with cancers that are caused by BRAFV600E gene mutations, including anaplastic thyroid cancer. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.



Surgical Options for Lymphedema

By Luanne Jorewicz

Lymphedema of the extremities, whether from cancer treatment or other causes, typically is not curable. But advances in surgical techniques are reducing or eliminating symptoms for many patients.

Standard treatments for lymphedema

The goal of standard lymphedema treatment is to manage the symptoms and either reduce swelling or halt its progression. Lymphedema treatment plans are tailored according to each patient's needs but commonly include compression garments, exercise, manual lymph drainage (a type of massage therapy), or combinations of these therapies. Health care providers also counsel patients who have lymphedema in proper skin care to guard against lacerations and infections.

Over the past century, various surgical techniques have been tried in an attempt to reduce or even cure lymphedema. However, most of these techniques have been abandoned because they are ineffective or the results could not be reproduced by other practitioners. Only recently have advances in microsurgery made the surgical management of lymphedema a viable alternative.

Surgery for lymphedema

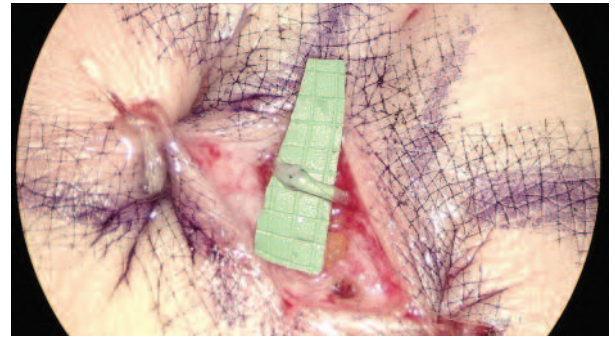
Since 2006, surgeons at The University of Texas MD Anderson Cancer Center have been performing microsurgical treatments for lymphedema—lymphovenous bypass and vascularized lymph node transfer—with promising results.

Specialists in Japan have been leading the advances in these procedures, and several surgeons from MD Anderson—including Roman Skoracki, M.D., and Matthew Hanasono, M.D., associate professors in the Department of Plastic Surgery—have spent time in Japan learning these skills. According to Dr. Skoracki, “It’s a treatment that hasn’t been readily accepted until the last 10 years or so, but it is now represented in several academic centers in the United States.” MD Anderson is still one of only about two dozen centers in the world that offer these advanced surgical procedures for lymphedema management, however.

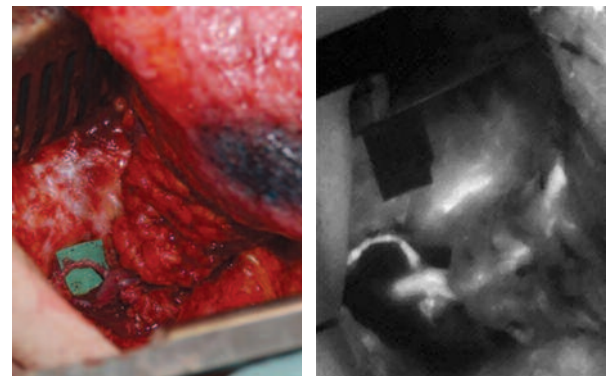
Any patient with lymphedema is a potential candidate for these microsurgical procedures, but the best results—particularly for lymphovenous bypass—are seen in patients with early-stage lymphedema. Active cancer is considered a contraindication to lymphedema surgery for most patients.

Because few institutions offer these procedures, no formal system has been established for selecting patients for the operations, so there are likely many patients who would benefit from one of the procedures who are not being referred to surgical teams for evaluation.

To plan for either of these microsurgical operations, the surgeons first stage the affected limb’s lymphatics by lymphoscintigraphy, in which a radioactive colloid is injected into the lymphatic vessels to



During a lymphovenous bypass, this lymphatic vessel smaller than 1 mm in diameter was anastomosed to an adjacent venule.



A vascularized lymph node transfer (left; center of image) to the axilla is performed simultaneously with a deep inferior epigastric perforator flap for breast reconstruction. Anastomoses are highlighted by a green background. Postoperative angiography (right) shows the perfusion of blood through the vascularized flap.

Research led by Dr. Hiroo Suami uses three-dimensional reconstructions of data from computed tomography scans with radiopaque media in the lymphatics of cadaveric specimens (left) to map lymphatic pathways (right). © 2014 Hiroo Suami, used with permission.

trace the flow of lymph and detect lymphatic dysfunction. Intraoperative lymphography is used during either procedure.

Lymphovenous bypass

In lymphovenous bypass, the surgeon anastomoses obstructed lymphatic vessels, typically 0.1 mm to 0.8 mm in diameter, to small adjacent venules so that lymph is redirected. The procedure, which requires two to five small incisions in the affected arm or leg, is usually performed using general anesthesia. Patients typically recover quickly; the procedure may take no more than a half day from arrival to discharge.

Although lymphovenous bypass can greatly reduce edema in the affected limb, most patients will continue to have some swelling after surgery and will continue standard lymphedema treatment with compression garments and massage therapy.

Lymph node transfer

A more invasive surgery is vascularized lymph node transfer. This procedure involves harvesting healthy lymph nodes from unaffected areas—often the groin for patients with lymphedema of the arm—and microsurgically transplanting them as vascularized flaps to replace damaged or missing lymph nodes.

“These lymph nodes are moved with an intact blood supply, an artery and a vein that can be anastomosed to the recipient site,” Dr. Hanasono said. “The transferred nodes then appear to absorb and collect the lymphatic fluid that was being blocked.”

The transferred lymph nodes are also thought to stimulate lymphangiogenesis, during which new lymphatic vessels grow and connect to the lymphatic channels of the transplanted lymph nodes to create new pathways for lymph drainage.

In some patients who have undergone delayed breast reconstruction with vascularized flaps, the lymph node transfer has been performed at the same time. Performing these two procedures simultaneously is becoming increasingly common, and the transferred lymph

nodes may be part of the same flap used for the breast reconstruction.

Because breast reconstruction with autologous flap transfer requires a hospital stay of approximately 5 days and lymph node transfer may require 2–3 days of in-hospital observation, performing the two procedures simultaneously saves the patient an additional trip to the hospital, a second operation under general anesthesia, recovery time, and considerable expense.

Patients typically wear compression garments for several weeks after undergoing lymph node transfer, but many are eventually able to stop using the garments. Infections that are common in patients with lymphedema are less frequent in patients who have undergone lymph node transfer or lymphovenous bypass, owing to the improved lymph drainage.

Exploring uncharted territory

One challenging aspect of lymph node transfer is to discern which nodes can be harvested without damaging the donor region and creating another area of lymphedema. To address this challenge, researchers at MD Anderson are remapping the lymphatic system and its drainage pathways—a field in which little has been done since the 19th century. Alexander Nguyen, M.D., an assistant professor in the Department of Plastic Surgery, is using lymphoscintigraphy and sentinel lymph node mapping to better identify critical lymph nodes that should be left intact.

By injecting dye into the hand, Dr. Nguyen is able to see where the lymphatics stagnate in the arm and to determine whether patients with upper extremity lymphedema would be better candidates for lymphovenous bypass or lymph node transfer. In addition, lymphoscintigraphy shows where the surgeons should be doing the anastomoses. Finding the appropriate lymphatic and an adequate vein used to be like finding a needle in a haystack, according to Dr. Nguyen. Now, he said, “We have a GPS to improve success rates.”

Research led by Hiroo Suami, M.D., Ph.D., an assistant professor in the Department of Plastic Surgery, also is

aimed at elucidating the anatomy of the circulatory system. Dr. Suami developed a unique technique using radiopaque media and a surgical microscope to visualize the lymphatic channels and to designate regional skin lymphatic zones called “lymphosomes.” When the lymphatic pathways are better understood, it may be possible to preserve a drainage route for the upper extremity via the clavicular lymph nodes (the Mascagni pathway), bypassing the axillary lymph nodes removed during axillary node dissections.

Also, Dr. Suami said, “The lymphosome concept will provide a template to more accurately interpret lymphoscintigraphy to diagnose cancer spread and define suitable lymph node donor sites for vascularized lymph node transfer.”

A better understanding of the lymphatic system will help surgeons to more effectively perform surgical procedures that reduce or even eliminate the symptoms of lymphedema. But even now, Dr. Nguyen said (paraphrasing the consensus statement of the International Society of Lymphology), “Microsurgery offers the closest chance to a cure for lymphedema that we currently have.” ■

FOR MORE INFORMATION

Dr. Matthew Hanasono.....713-794-1247
Dr. Alexander Nguyen.....713-794-1247
Dr. Roman Skoracki713-794-1247
Dr. Hiroo Suami713-794-1247

ADDITIONAL RESOURCES

Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg.* 2013;132:1305–1314.

Video: Lymphaticovenular Bypass Surgery Explained. http://www3.mdanderson.org/streams/FullVideoPlayer.cfm?xml=communications/config/LymphaticovenularBypassSurgery-540_cfg

Intensity-Modulated Radiation Therapy Improves Survival in Head and Neck Cancer Patients

Compared with conventional radiation therapy, intensity-modulated radiation therapy (IMRT) is associated with a significantly higher cause-specific survival rate in patients with head and neck cancers, according to a recent study. The study is the first to suggest that IMRT improves survival outcomes in head and neck cancer patients.

“Previous studies indicated that patients treated with IMRT did better when it came to treatment-related side effects; however, these studies were not designed to examine survival,” said Beth Beadle, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center and the first author of the study’s report. “IMRT is intended to spare normal tissues but still deliver radiation to the tumor, so previous models assumed survival was equivalent to survival with conventional radiation therapy.”

Using the Surveillance, Epidemiology, and End Results–Medicare database, Dr. Beadle and her colleagues identified 3,172 patients who received either conventional radiation therapy (2,116 patients) or IMRT (1,056 patients) for head and neck cancer of any subtype between 1999 and 2007.

“[T]he findings support the use of IMRT and suggest we can provide excellent care while optimizing cancer outcomes and reducing toxicities.”

– Dr. Beth Beadle

The researchers found that at a median follow-up of 40 months, the cause-specific survival rate of the patients who received IMRT (84%) was significantly higher than that of the patients who received conventional radiation therapy (66%; $P < .001$). The difference remained even after adjustment to account for sources of potential bias.

“From a scientific perspective, the findings support the use of IMRT and suggest we can provide excellent care while optimizing cancer outcomes and reducing toxicities,” Dr. Beadle said. “From the perspective of health care financing and resource allocation, IMRT is more expensive than conventional radiation therapy, but the data suggest it’s worth it.”

The study was reported in the journal *Cancer* in March. ■

Research Findings Could Lead to Blood Test for Cancer-Related Gene Defects

Some surprising research findings suggest that a simple blood test could be developed to detect gene mutations associated with cancer and thus guide treatment. Such a test might also facilitate the early diagnosis of pancreatic cancer and other cancers that often are asymptomatic until they become advanced and difficult to treat.

“At the present time, there is no single blood test that can screen for all cancer-related DNA defects,” said Raghu Kalluri, M.D., Ph.D., a professor in and chair of the Department of Cancer Biology at The University of Texas MD Anderson Cancer Center.

As the first step toward developing such a test, Dr. Kalluri and his research team investigated exosomes, which are tiny vesicles shed into the serum by many types of cells—including cancer cells. It was known that exosomes play a role in intercellular signaling and that they carry single-strand DNA frag-

ments. Dr. Kalluri’s team hypothesized that exosomes also contain double-stranded genomic DNA, which could reveal cancer-related gene mutations.

To test their hypothesis, the researchers performed polymerase chain reaction analyses and whole-genome sequencing on exosomes from two human pancreatic cancer cell lines and from blood samples from patients with pancreatic cancer and healthy volunteers. The two cancer cell lines, Panc-1 and T3M4, both are known to harbor *KRAS* and *TP53* mutations.

The researchers found *KRAS* and *TP53* mutations in the exosomes from cancer cells and from pancreatic cancer patients’ blood samples. The mutations were not found in the exosomes from healthy volunteers’ blood samples.

“Because different forms of cancer are associated with different chromosomal mutations, we believe analysis of exosome DNA taken from blood samples may not only help determine the presence of a cancerous tumor somewhere in the body but also identify mutations without the need for a tumor sample,” Dr. Kalluri said.

The research was reported in the *Journal of Biological Chemistry*. ■

Tumor-Suppressing Protein May Help Predict Survival in Some Breast Cancer Patients

The tumor-suppressing protein ZMYND11 may help predict survival in patients with triple-negative breast cancer and possibly other tumors.

A study led by Xiaobing Shi, Ph.D., an assistant professor in the Department of Biochemistry and Molecular Biology at The University of Texas MD Anderson Cancer Center, identified ZMYND11 as a histone reader protein that specifically recognizes methylated histones and prevents uncontrolled transcription. To do this, Dr. Shi and his colleagues performed

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Sleep Problems in Cancer Patients

Sleep disorders can be managed



Getting a good night's rest is important for everybody, especially cancer patients, who often experience fatigue from the disease or its treatment.

Sleep disorders can impair cancer patients' quality of life and even treatment outcomes, but fortunately these disorders can usually be managed.

Sleep disorders and their effects

According to the National Cancer Institute, as many as half of patients with cancer report some type of sleep disorder.

- The five major sleep disorders are
- insomnia, the inability to fall asleep and stay asleep;
 - sleep apnea, breathing stops of 10 seconds or more during sleep;
 - hypersomnia, difficulty staying awake during the day;
 - circadian rhythm disorder, the inability to sleep and wake at the right times; and
 - parasomnia; acting in unusual ways—for instance, walking, talking, or eating—while falling asleep, sleeping, or waking from sleep.

The most common sleep disorders in cancer patients are circadian rhythm disorder and insomnia. In fact, cancer patients are twice as likely to experience insomnia as are people without cancer. Sleep apnea also is more common among cancer patients than in the general population and may be caused by the location of the tumor or side effects of medications.

Sleep problems can be made worse by many cancer-related factors, including pain, anxiety, depression, side effects of treatment, and overnight hospital stays.

Unfortunately, poor sleep can have a negative impact on cancer treatment. Cancer patients who are not sleeping well may feel pain more intensely and may have more trouble tolerating some

treatments than do well-rested patients. Because sleep affects the immune system, sleep disruption may also reduce the body's ability to fight infection.

Managing sleep problems

To determine whether a cancer patient has a sleep disorder, a doctor will per-

form a physical examination and take a medical history, asking about daytime and sleep habits, exercise routine, and medications. Sometimes a sleep test called polysomnography will be given. Conducted during an overnight stay at a sleep center, the test provides information about the patient's sleep stages, blood oxygen levels, breathing, muscle tone, heart rate, and general sleep behavior.

Fortunately, most sleep problems can be treated.

A person suffering from sleep apnea might be treated with a continuous positive airway pressure device, a face mask that helps keep the airway open during sleep. Other sleep disorders might be addressed by taking prescription medications, by making lifestyle changes that promote better sleep, by treating another illness that contributes to the sleep problem, or by relieving side effects of cancer or cancer treatment that disrupt sleep.

Medications for insomnia are usually only a short-term solution. More effective in the long run are managing stress and anxiety and treating a patient's fatigue.

Cognitive behavioral therapy (CBT) also has proven effective in treating insomnia while reducing by half the need for sleep medications by cancer patients. CBT helps reduce anxiety about getting enough sleep.

Depending on the patient's needs, CBT may include stimulus control therapy, which trains the patient to associate the bedroom only with sleep; relax-

ation therapy, which teaches techniques such as progressive muscle relaxation and guided imagery to relieve muscle tension and stress; and sleep hygiene, which teaches behaviors that promote healthy sleep. The new behaviors could include developing a relaxing bedtime ritual; getting out of bed if sleep is difficult and returning only when sleepy; and making the bed and bedroom more conducive to sleep by controlling light, temperature, and noise.

The American Cancer Society offers several tips that people with cancer can use to ensure they get a good night's rest:

- Sleep as much as your body tells you to.
- Try to exercise at least once a day, but don't exercise close to bedtime.
- Avoid alcohol in the evening and caffeine for 6–8 hours before bedtime.
- Drink warm, caffeine-free drinks, such as warm milk or decaffeinated tea, before sleep.
- Go to sleep in a quiet setting at the same time each night.
- Take prescribed pain relievers or sleeping medicine at the same time each day.
- Keep bed sheets clean and neatly tucked in.
- Have someone rub your back or massage your feet before bedtime.

Cancer patients should discuss any sleep problems with their health care team. Resolving sleep issues can improve a patient's response to cancer treatment and address some related health problems such as high blood pressure. In addition, getting regular restorative sleep can improve a patient's daily quality of life, immune system, and cognitive abilities. ■

– K. Stuyck

FOR MORE INFORMATION

- Talk to your physician and request a consult with a sleep physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789

ADDRESS SERVICE REQUESTED

IN BRIEF

[Continued from page 6]

a detailed structural analysis, cell line and mouse experiments, and analyses of human tumor specimens.

During normal gene expression, transcription of an expressed gene is performed by RNA polymerase II. As RNA polymerase II travels along the DNA, a group of proteins associated with the polymerase leaves behind histone markers that serve as “placeholders” to indicate which regions of the gene have been transcribed. These markers serve several purposes, many of which have yet to be fully characterized in humans.

Methylation is one of the most common histone markers and can serve a wide variety of purposes. Dr. Shi’s group found that ZMYND11 binds to a specific type of methylated histone (H3.3) and then prevents a critical step in transcription.

By preventing the transcription of genes marked with methylated H3.3, ZMYND11 is able to repress the aberrant expression of oncogenes in preclinical malignancies. ZMYND11 may also help activate genes that encode other tumor-suppressing proteins, but that function is less clear.

To understand how ZMYND11 affects cancer cell growth, the researchers expressed ZMYND11 in a triple-negative breast cancer cell line. Expression of normal ZMYND11 suppressed tumor cell growth, but when Dr. Shi’s group modified ZMYND11 to prevent it from binding to

ZMYND11 may be an important prognostic marker for patients with triple-negative breast cancer and possibly other cancers.

methylated H3.3, it was unable to suppress growth. Similarly, mice injected with tumor cells expressing normal ZMYND11 had much smaller tumors than those injected with cells expressing non-functional ZMYND11.

Because they found such striking results in mice, Dr. Shi’s group decided to survey ZMYND11 expression levels in triple-negative breast cancer specimens. The researchers analyzed tumor samples from 120 patients with triple-negative breast cancer and found that women whose tumors expressed high levels of ZMYND11 had an 80% 10-year disease-free survival rate, whereas those women whose tumors expressed low levels of ZMYND11 had a 50% disease-free survival rate.

These findings, which were published in *Nature* in April, indicate that ZMYND11 may be an important prognostic marker for patients with triple-negative breast cancer and possibly other cancers. ■

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