OncoLog
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Striving to Improve Treatments for Uveal Melanoma

By Bryan Tutt

Although primary uveal melanoma can be effectively treated with radiation or surgery, patients with metastatic disease—or those at high risk for metastases—have few proven options. But specialists in medical oncology, radiation oncology, ophthalmology, surgery, and translational research are working to improve those options.

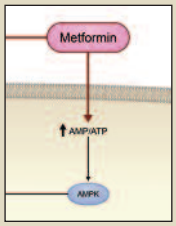
Uveal melanoma is rare and accounts for only about 5% of melanoma cases; however, metastatic disease from uveal melanoma is often fatal because the most common metastatic site is the liver. Even among patients who have no evidence of disease after treatment of the primary tumor, metastatic disease will occur in about 25% within 5 years and 50% at some point in their lives.

In an attempt to minimize the risk of death from metastatic disease in patients with uveal melanoma, physicians and scientists at The University of Texas MD Anderson Cancer Center are pursuing a multidisciplinary strategy that includes treating the primary tumor, identifying patients at high risk of metastatic disease and providing them with adjuvant therapy or increased surveillance, and exploring new treatments for metastatic disease.

Treating the primary tumor

Treatment of the primary tumor requires surgery, i.e., the removal of the eye, in about 30% of patients with uveal melanoma. Most patients can instead be treated with brachytherapy, in which a radioactive plaque is implanted in the patient and remains in place for 2–4 days, depending on the size of the tumor. According to Beth Beadle, M.D., an assistant professor in the Department of Radiation Oncology, brachytherapy achieves local control

***Dr. Dan Gombos** prepares to insert a radioactive plaque in a patient with uveal melanoma. For most patients, plaque brachytherapy enables local control of the primary tumor without removal of the globe.*



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in approximately 90% of patients with uveal melanoma in whom it is used. Iodine 125 is the most commonly used isotope in brachytherapy for uveal melanoma.

Another isotope used to treat the disease is ruthenium 106, which was available in the United States from 2003 until 2007, when it became unavailable on the U.S. market for commercial reasons. However, ruthenium 106 has remained available in other countries and is widely used in Europe. "Ruthenium gives a very high radiation dose to a very small area—even more so than iodine—so the toxicity to normal tissues tends to be less," Dr. Beadle said.

Ruthenium 106 recently became available again in the United States, and MD Anderson was among the first institutions in the nation to resume its use. The decision to reinstate its use at MD Anderson was based on a review of 40 patients treated with ruthenium 106 plaque brachytherapy for uveal melanoma at the institution between 2003 and 2007. In the review, Dr. Beadle and her colleagues found that ruthenium 106 achieved local control equivalent to that of iodine 125 but with fewer toxic effects.

"Because of the narrow depth of penetration of the radiation, we can only use ruthenium for very small lesions, those less than 5 mm in depth; but that describes the majority of lesions we see," Dr. Beadle said. "Iodine is still a very good treatment, but for patients with very small tumors, ruthenium seems to be even better."

Tumors diagnosed early are likely to be small enough to be treated with ruthenium 106. "If we catch these tumors early, we can salvage the globe and also offer the patients a treatment that causes less toxicity to the eye," said Dan Gombos, M.D., a professor in the Department of Head and Neck Surgery and chief of the Section of Ophthalmology. While early diagnosis increases treatment options for the primary tumor, whether early treatment decreases a patient's chance of developing metastatic disease is unknown.

> **"[T]here are no known common mutations between uveal and cutaneous melanoma. Uveal melanoma has its own subset of unique genomic characteristics."**
>
> **– Dr. Elizabeth Grimm**

Assessing the risk of metastases

"There are two schools of thought about metastases from uveal melanoma," Dr. Beadle said. "One is that the longer the patient has uncontrolled local disease, the greater the opportunity for it to spread; and the other is that metastatic disease is determined by the tumor's biology and isn't affected by what is done to control local disease."

The effect of tumor biology on the development of uveal melanoma metastases has been elucidated in recent years. A commercially available test (DecisionDx-UM, Castle Biosciences) analyzes tumor RNA for a group of gene mutations associated with a high risk of uveal melanoma metastasis. This gene expression profile is used to classify a patent's risk of developing metastases after successful treatment of the primary tumor.

"About 50% of the patients identified by the test as having high-risk disease go on to develop metastases by 3 years after treatment, and more than 70% develop metastases by 5 years," said Sapna Patel, M.D., an assistant professor in the Department of Melanoma Medical Oncology.

One limitation of the test is that it requires a tumor sample, which in most patients must be obtained by a needle biopsy. Because uveal melanoma is diagnosed on the basis of clinical features, a biopsy historically was considered unnecessary. "Twenty years ago, we never biopsied these tumors," Dr. Gombos said, adding that this philosophy is changing and that many ocular oncologists and ophthalmologists perform a needle biopsy before sewing on the radiation plaque. "There was a concern that a needle biopsy might increase the risk of disease spread, but the consensus now is that this risk is exceptionally low."

Another limitation of the test is that physicians have few options for patients whose tumors are identified as high risk. "This test is highly prognostic in terms of telling people they're going to have a bad outcome," Dr. Patel said. "The problem is that in uveal melanoma, not only is there no standard of care for metastatic disease, there are no proven effective adjuvant therapies."

Toward effective adjuvant therapy

After local control of the primary tumor has been achieved, all uveal melanoma patients at MD Anderson—especially those whose gene expression profile indicates a high risk of metastasis—are referred to Dr. Patel or one of her colleagues in the Department of Melanoma Medical Oncology for a consultation. The oncologists offer the options of surveillance (the standard of care) or experimental or off-protocol adjuvant therapy aimed at destroying micrometastases before clinically detectable metastatic disease can develop in the liver or elsewhere.

Dr. Patel was the principal investigator for a clinical trial of adjuvant therapy for patients who had been treated for primary uveal melanoma and had a high risk of metastases. Patients in the study were given ipilimumab to boost the immune system's surveillance for cancer. The trial is no longer enrolling patients because of funding issues.

For patients with a high risk of metastasis after primary treatment of uveal melanoma, the off-label use of ipilimumab for adjuvant therapy is generally unfeasible. "Right now ipilimumab is one of the most expensive agents in cancer medicine, and it is not approved for adjuvant therapy," Dr. Patel said. "Insurance companies would pay for treatment if a patient has metastatic disease, but these patients don't have

metastatic disease; they are at high risk of developing metastasis." However, other off-protocol adjuvant approaches often are used to treat such patients.

Because metastatic uveal melanoma most commonly emerges in the liver, one off-protocol approach is liver-directed therapy. "The idea is that there might be micrometastases in the liver that we can't detect on a computed tomography scan. The tumor burden we suspect would be extremely small, so we bathe the liver in chemotherapy drugs to wipe out the tumors," Dr. Patel said.

In liver-directed therapy, an interventional radiologist inserts a catheter through the groin into the hepatic circulation to deliver chemotherapeutic agents. Treatments alternate so that one round of chemotherapy infuses the right side of the liver and the next round infuses the left side.

Another approach to adjuvant therapy is to restore BAP1 protein function with histone deacetylase inhibitors such as vorinostat; inactivating mutations in the *BAP1* tumor suppressor gene are common in uveal melanoma and indicate a high risk of metastasis. Dr. Patel said that valproic acid, which is commonly used to treat seizures, also inhibits histone deacetylase and is inexpensive. However, she added, "It's not clear what dose of valproic acid would be needed to prevent uveal melanoma metastases via histone acetylation."

Treating metastatic disease

As with adjuvant treatment for uveal melanoma, much is yet to be learned about treatment for metastatic disease. "Once a patient has metastases in the liver, it's very challenging to cure the disease," Dr. Gombos said. "There are some classes of drugs that we are excited about, but we don't have a proven treatment for metastatic disease."

In a phase II trial under way at MD Anderson and other centers, patients with metastatic uveal melanoma are randomly assigned to receive the MEK inhibitor trametinib with or without the AKT inhibitor GSK2141795. "The MEK and AKT pathways seem complementary in driving metastatic disease, so blockade of both should be important," Dr. Patel said.

A clinical trial of an anti–PD-L1 antibody for patients with metastatic uveal melanoma recently completed enrollment, but more trials dedicated to metastatic uveal melanoma will open soon at MD Anderson. Also, patients with metastases from uveal melanoma may be eligible for several open studies enrolling patients with various cancer types.

Ongoing research

In addition to clinical studies, basic science and translational research play important roles in the search for ways to prevent or cure metastasis from uveal melanoma.

Although anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies have extended survival durations for patients with metastatic cutaneous melanoma (see "New Approaches Revolutionize the Treatment of Advanced Melanoma," *OncoLog*, February 2014), the effects of these drugs in uveal melanoma patients are not as well known.

Elizabeth Grimm, Ph.D., a professor in the Department of Melanoma Medical Oncology, explained that uveal melanoma does not always respond to the agents that are effective against cutaneous melanoma because the two diseases are biologically distinct. "To date, there are no known common mutations between uveal and cutaneous melanoma," Dr. Grimm said. "Uveal melanoma has its own subset of unique genomic characteristics, notably chromosome 3 monosomy."

Understanding uveal melanoma's genomic characteristics and finding agents that can exploit them is a major goal for Dr. Grimm and other investigators in the Department of Melanoma Medical Oncology. For example, Scott Woodman, M.D., Ph.D., and Chandrani Chattopadhyay, Ph.D., are planning a major drug screening—a template of 6,000 drugs—with the Gulf Coast Consortia. The researchers have developed protocols for testing the activity of various classes of drugs against uveal melanoma samples in vitro.

In addition to the drug screening, Dr. Chattopadhyay is investigating the effects of hepatocyte growth factor and insulin-like growth factor receptor on liver metastases from uveal melanoma in vitro. "These specific growth factors and receptors cause things to grow in the liver, so we're studying primary uveal melanomas and liver metastases for their dependence on these factors," Dr. Grimm said.

For the projects described above and others, Dr. Grimm and her colleagues—including Bita Esmaeli, M.D., a professor in the Department of Plastic Surgery—have been collecting blood and tumor samples from uveal melanoma patients for 15 years. Many of these tumors have been submitted to The Cancer Genome Atlas for analysis.

Dr. Grimm said the rarity of uveal melanoma and the small size of biopsy samples limit researchers' resources, but she and her colleagues overcome these challenges through multi-institutional collaboration. "We have a worldwide network of laboratories," she said. "It's a very active field. We're one of the leading centers for uveal melanoma, but we collaborate with centers around the world."

Anticipating a new era

Although currently physicians have limited options to offer patients with metastatic uveal melanoma or a high risk of developing metastases, Dr. Gombos is optimistic. He said, "I think we're at the crossroads of a new era in uveal melanoma where we can begin to offer directed therapy with better options than in the past. MD Anderson has assembled a truly unique multidisciplinary team of clinicians and researchers at the forefront of this rare ocular malignancy." ■

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Beyond Diabetes: Metformin May Have

By Sunita Patterson

Metformin, an inexpensive drug that has been prescribed for diabetes for decades, may also be useful in preventing or treating several types of cancer.

Since its 1995 approval by the U.S. Food and Drug Administration, metformin has become one of the most commonly prescribed medications for type 2 diabetes, but the drug has potential for other uses. Metformin is also being tested for treating prediabetes, polycystic ovary syndrome, and various cancers. If metformin's efficacy in cancer treatment is proven, cancer patients may benefit not only medically but also financially—a month's supply of the generic form of this oral medication costs less than $5 at many U.S. pharmacies.

Aung Naing, M.D., an associate professor in the Department of Investigational Cancer Therapeutics, is one of several researchers at The University of Texas MD Anderson Cancer Center who are currently leading studies of metformin. "This oldie for endocrinologists is the new kid on the block for oncologists," he said.

Early results in many cancers

Dr. Naing cited two 2009 publications by MD Anderson researchers that alerted him to metformin's potential anticancer activity. In the first study, a group in the Department of Breast Medical Oncology noticed that among 2,529 women with early-stage breast cancer, the pathological complete response rate after chemotherapy was higher (24%) in diabetic patients who had received metformin than in diabetic patients who had not received metformin (8%) and in nondiabetic patients (16%). In the second study, a group in the Department of Gastrointestinal Medical Oncology found that among 255 diabetic patients, the risk of developing pancreatic cancer was 62% lower in those who received metformin than in those who did not.

Since that time, researchers at MD Anderson have conducted several retrospective studies looking at outcomes of patients who had concurrent cancer and diabetes. In separate studies of patients who had prostate cancer, colorectal cancer, pancreatic cancer, triple-negative breast cancer, HER2-positive breast cancer, and multiple myeloma, the median overall survival durations were found to be longer in patients who had taken metformin than in those who had not.

Myriad molecular effects

At the translational research level, in vitro and in vivo studies have supported the use of metformin in several cancer types and, along with tumor specimen biomarker studies, have begun to elucidate the molecular mechanisms of metformin's action.

Metformin seems to affect multiple key processes related to cell growth, proliferation, and survival. The drug's effects on these processes stem from both metabolic and intracellular-signaling activity. First, metformin decreases the amount of glucose produced by the liver and reduces the bloodstream level and cellular uptake of insulin. In turn, the reduced insulin stimulation results in reduced activation of insulin receptors on cell membranes, triggering a cascade of intracellular molecular effects (see figure, page 5), such as the downregulation of the Ras/Raf/MEK/ERK and PI3K/AKT/mTOR signaling pathways. One or both of these pathways are often activated in many types of cancer cells. In addition, metformin appears to upregulate AMP-activated protein kinase, a key molecule in glucose and insulin regulation and also an inhibitor of mTOR.

Clinical trials

On the basis of retrospective and preclinical studies that indicated metformin's potential as an anticancer agent, the drug is now being combined with traditional chemotherapy, radiation therapy, targeted therapy, and other cancer treatments in clinical trials. Metformin is also being studied in a single-agent cancer prevention trial. At the time of this writing, MD Anderson has six open clinical trials involving metformin (see "Clinical Trials," page 6), with several more under development.

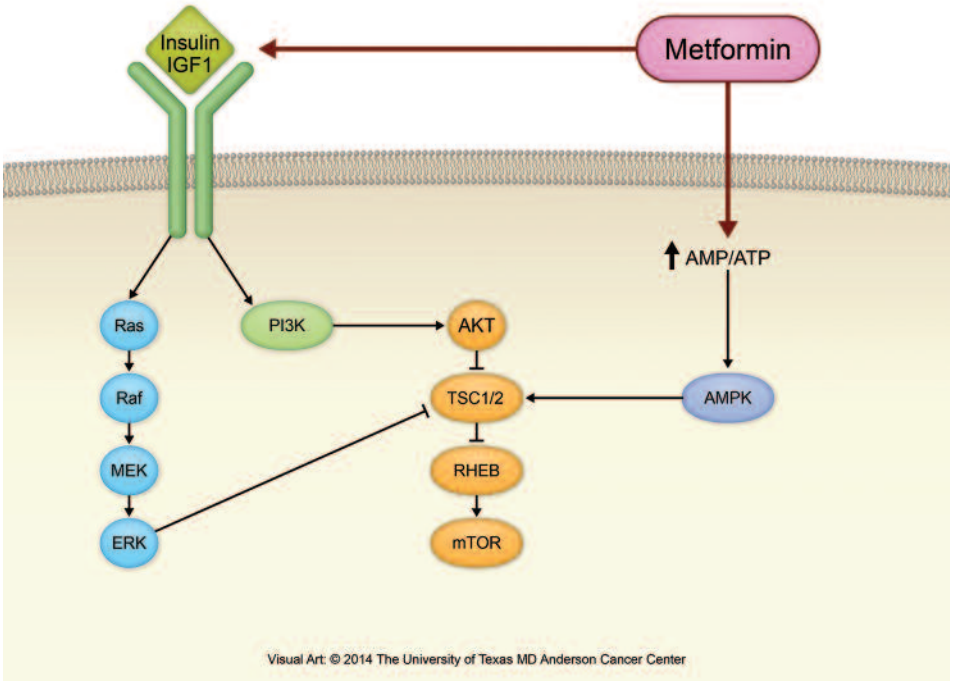
Metformin in endometrial cancer

The link between diabetes and endometrial cancer makes metformin attractive as a potential treatment for the cancer. "Insulin resistance and diabetes are two of the main risk factors for endometrial cancer, and obesity—which is often seen with diabetes—increases the risk of endometrial cancer more than any other cancer," said Pamela Soliman, M.D., M.P.H., an associate professor in the Department of Gynecologic Oncology and Reproductive Medicine.

Several molecular pathways affected by metformin come into play in endometrial cancer—in particular, the PI3K/AKT/mTOR pathway. For this reason, Drs. Naing and Soliman are leading clinical trials combining metformin with another mTOR inhibitor. "If you block the same pathway with two mechanisms, you may get an additive effect," said Dr. Soliman.

Dr. Soliman's current phase II trial combines metformin with the mTOR inhibitor everolimus and the anti-estrogen agent letrozole for the treatment of advanced or recurrent endometrial cancer. This trial derived from an earlier trial in which patients received everolimus and letrozole. "A patient in that first trial developed diabetes, which is a side effect of mTOR inhibitors, and her primary care physician started her on metformin," Dr. Soliman said. "The patient had had stable disease before metformin, but with metformin she started responding to the study drugs. Then I had another patient who was taking metformin and also started

Broad Utility in Cancer



Metformin affects cell signaling pathways directly or indirectly at multiple points. For this reason, the drug may be useful against numerous cancer types.

responding to the cancer treatment."

Dr. Soliman's clinical observations prompted her to look at metformin in the lab; her group found in cell lines and mice that metformin decreased endometrial cancer cell growth. Next, the researchers looked at biomarkers in endometrial cancer patients' baseline diagnostic biopsy specimens and post-metformin surgical specimens. Dr. Soliman reported on the molecular changes in these specimens at the 2014 American Society of Clinical Oncology Annual Meeting.

In addition to leading the everolimus/letrozole/metformin study, Dr. Soliman is the principal investigator at MD Anderson for a national trial for patients with stage III or IV endometrial cancer. One group of patients will be randomly assigned to receive standard-of-care chemotherapy (paclitaxel and carboplatin); the other group will receive those drugs plus metformin.

Dr. Naing's combination treatment trial pairs metformin with the mTOR inhibitor temsirolimus. The trial's first phase has enrolled patients with many types of advanced cancer, and the second phase will focus on patients with endometrial cancer. Dr. Naing has incorporated two innovative aspects into this trial.

First, Dr. Naing is using a dose-titration strategy that may ultimately allow higher doses of the drugs to be safely given than previous trials achieved. "Metformin is started at a low dose and gradually increased to a higher dose," Dr. Naing said. "Then temsirolimus is started. In the first phase of the trial, this strategy reduced the side effects. And since one of the side effects of temsirolimus is hyperglycemia, which is treated with metformin, we are hitting two birds with one stone."

A second innovation in the trial is that serial biopsy specimens will be collected from patients whose endometrial cancers have gene mutations that affect the PI3K/AKT/mTOR pathway. "A high frequency of mutations affecting this pathway is seen in endometrial cancer," Dr. Naing said. Because metformin and temsirolimus both inhibit this pathway, he is interested to see whether changes will occur over time in the molecular profiles of the biopsied tissues.

Dr. Naing also hopes to learn whether the response to metformin is better in patients with certain mutations than in patients without the mutations. "We think it will be a signature trial for women with endometrial cancer," Dr. Naing said.

Metformin in lung cancer

Two clinical trials combining metformin and radiation therapy for lung cancer will be opening soon.

Metformin's effects on metabolism brought it to the attention of Heath Skinner, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology. "One possible means of resistance to radiation is altered tumor metabolism," said Dr. Skinner, whose group conducted in vitro and in vivo experiments suggesting that metabolically targeted drugs such as metformin would work as radiosensitizers. His next step was retrospective chart reviews looking at patients who were treated with radiation therapy and whether they were taking metformin. "In many of the populations we looked at—patients with head and neck, esophageal, and lung cancer—the patients taking metformin for their diabetes had a better outcome."

On the basis of those results, Dr. Skinner is finalizing approval for a National Institutes of Health–funded clinical trial of stereotactic radiation therapy plus metformin for patients with inoperable stage IB non–small cell lung cancer. Patients will undergo a baseline positron emission tomography (PET) scan, receive metformin or placebo for 3 weeks, have another PET scan, and then continue the drug during radiation treatment; a third PET scan will be performed after 6 months. Dr. Skinner said, "We will be able to see whether metformin by itself affects the size of tumors seen on the PET scan and whether metformin plus radiation improves the outcome over radiation alone."

Dr. Skinner is also a co–principal investigator on a national phase II trial sponsored by NRG Oncology, a nonprofit research organization. In this

Metformin May Have Broad Utility in Cancer

[Continued from **page 5**]

trial, which will soon be enrolling patients at MD Anderson, patients with locally advanced non–small cell lung cancer will be randomly selected to receive the standard-of-care treatment, chemoradiation, with or without metformin. "These two studies are the only ones I'm aware of that are combining metformin with radiation therapy," Dr. Skinner said.

Benefits and cautions

Metformin's utility for cancer patients may extend beyond treatment and prevention. A group in MD Anderson's Department of Symptom Research is studying whether the drug relieves chemotherapy-induced peripheral neuropathy. A recent preclinical study by the group showed that giving mice metformin along with cisplatin (compared with placebo and cisplatin) significantly reduced loss of paw sensitivity and protected peripheral-nerve endings.

Despite metformin's many potential benefits in cancer treatment and prevention, Dr. Naing cautioned that the drug's use for cancer is still investigational. Robust clinical trials such as the ones under way are needed to ensure safety and efficacy.

Some precautions must be taken when prescribing metformin. Although very rare, lactic acidosis can occur with metformin use, particularly in patients with renal issues, so the drug is not recommended in patients with abnormal renal or hepatic function; nor is it prescribed in patients with heart failure. Also, metformin must be discontinued before the administration of an imaging contrast agent. Finally, metformin should be combined with other drugs with care.

These contraindications notwithstanding, metformin is widely used as an antidiabetic agent because its adverse effects are usually quite manageable; diarrhea, nausea, and vomiting are the most common. "The good thing about metformin," Dr. Skinner said, "is it's extraordinarily safe, it's extraordinarily inexpensive, and it should be able to easily be integrated into cancer therapy." ■

FOR MORE INFORMATION

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Dr. Pamela Soliman.....713-745-2352

FURTHER READING

Hajjar J, Habra MA, Naing A. Metformin: an old drug with new potential. *Exp Opin Invest Drugs.* 2013;22:1511–1517.

CLINICAL TRIALS: Metformin

A phase I study of temsirolimus in combination with metformin in patients with advanced cancers (2011-0923). Principal investigator (PI): Dr. Aung Naing. The goal of this study is to find the highest tolerable doses of metformin and temsirolimus in patients with advanced cancer. The safety and effects of the drug combination will also be studied.

A phase I trial of lapatinib in combination with sirolimus or metformin in advanced cancer (2009-0743). PI: Dr. Filip Janku. The goal of this study is to find the highest tolerable doses of two different drug combinations in patients with advanced cancer. One group will receive lapatinib and sirolimus; a second group, lapatinib and metformin. The safety and effects of these drug combinations will also be studied.

A phase I lead-in to a 2 × 2 × 2 factorial trial of temozolomide, memantine, mefloquine, and metformin as postradiation adjuvant therapy of glioblastoma multiforme (2011-0374). PI: Dr. Marta Penas-Prado. The goal of this study is to find the highest tolerable doses of temozolomide in combination with memantine, mefloquine, and/or metformin that can be given to patients with glioblastoma who have already had radiation and chemotherapy. The safety of these drug combinations will also be studied.

An endometrial cancer chemoprevention study of metformin versus no treatment in women with a body mass index ≥ 30 kg/m^2 and hyperinsulinemia (2011-0739). PI: Dr. Karen Lu. The goal of this phase III study is to learn about the effects on the endometrium of metformin versus placebo, with and without a lifestyle (diet and exercise) intervention, in obese, postmenopausal women. Levels of insulin and cancer-associated biomarkers will be studied.

A phase II, single-arm study of RAD001 (everolimus), letrozole, and metformin in patients with advanced or recurrent endometrial carcinoma (2012-0543). PI: Dr. Pamela Soliman. The goal of this study is to learn whether the combination of everolimus, letrozole, and metformin can help control recurrent or progressive endometrial cancer. The safety of this drug combination will also be studied.

A randomized phase II/III study of paclitaxel/carboplatin/metformin versus paclitaxel/carboplatin/placebo as initial therapy for measurable stage III or IVA, stage IVB, or recurrent endometrial cancer (GOG0286B). PI: Dr. Soliman. The purpose of this study is to find out whether the drug combination of paclitaxel, carboplatin, and metformin works better than paclitaxel and carboplatin alone against advanced endometrial cancer and to find out what side effects are caused by treatment with these drugs. This study is being sponsored by the Gynecologic Oncology Group, a collaborative organization funded by the U.S. National Cancer Institute to oversee multicenter clinical research. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.

Smoking Cessation

Medications help smokers quit

You probably already know that smoking is the leading cause of lung cancer. And you may also know that smoking contributes to heart disease, stroke, and lung diseases such as emphysema. But did you know that even patients who have been diagnosed with these diseases greatly benefit from stopping smoking? And if you're trying to quit smoking, did you know that over-the-counter aids and prescription medicines are available to help you?

Benefits of quitting

Quitting smoking has both short-term and long-term benefits. Within a few months of quitting, most former smokers have improved blood circulation and lung function as well as less coughing.

As a group, former smokers who have not smoked for 1 year have just half the risk of heart disease as that of smokers, and at 5 years the risk becomes the same as that of lifelong nonsmokers. Former smokers who have not smoked for 5 years have half the risk of smoking-related cancers (lung, mouth, throat, esophagus, cervix, and bladder cancers) as that of smokers, and at 15 years former smokers' risk for these cancers becomes the same as that of lifelong nonsmokers.

Even after a cancer diagnosis, it's not too late to stop smoking. Studies have shown that lung cancer patients who continue smoking while undergoing treatment have more severe side effects, lower rates of response to therapy, lower 5-year survival rates, and a higher risk of secondary cancers or lung cancer recurrence than patients who quit.

Aids to help you quit

Quitting smoking is important but isn't easy. Nicotine, the substance in cigarettes that keeps you addicted, is extremely powerful. And the behaviors associated with smoking are deeply ingrained in daily life. Overcoming a tobacco addiction takes determination, but you don't have to rely on willpower alone. Here are some of the aids available to help you quit.

Nicotine replacement therapies

Nicotine replacement therapies slowly wean you from your nicotine addiction by providing controlled doses of nicotine, which you can lower over time. As your body adjusts to lower and lower doses of nicotine, your cravings for cigarettes and your symptoms of withdrawal will decrease. Studies have shown that nicotine replacement therapy can double your chances of successfully quitting smoking. These therapies are considered relatively safe because they don't contain the cancer-causing chemicals and harmful compounds found in tobacco.

Common nicotine replacement therapies such as patches, gum, and lozenges are available without a prescription and can be purchased at pharmacies and grocery stores. The nicotine patch is the easiest option for heavy smokers because it delivers a steady stream of low-dose nicotine. The gum and lozenges provide relief for withdrawal and keep your mouth busy without a cigarette and are especially helpful for people who habitually smoke at certain times, such as after dinner or with their morning coffee.

Electronic cigarettes (e-cigarettes) resemble cigarettes but do not contain tobacco. The doses of nicotine and other additives vary among e-cigarette brands. The safety of e-cigarettes has not been established, and e-cigarettes are not approved as a nicotine replacement therapy by the U.S. Food and Drug Administration.

Some nicotine replacement therapies are available by prescription. The nicotine nasal spray is like a nasal spray you might use for a stuffy nose or allergies. It delivers a fast-acting single dose of nicotine and can be used on a schedule or at the moment a craving hits. The nicotine inhaler is placed in the mouth, and the nicotine is absorbed in your mouth as you puff. Like the nasal spray, it delivers a fast-acting, measured dose of nicotine.

When considering your options for nicotine replacement therapy, keep in mind that—like cigarettes—these agents contain nicotine, which can cause side effects in some people. Talk to your doctor before using any nicotine replacement therapy.

Non-nicotine medications

Your doctor may prescribe a non-nicotine medication to be used instead of or along with nicotine replacement therapy. These medications reduce nicotine cravings and withdrawal symptoms, and studies have shown that smokers who use non-nicotine drugs are more likely to quit than those who don't take the medications.

Bupropion (Zyban) and varenicline (Chantix) are the most commonly prescribed non-nicotine drugs for smoking cessation. Some people taking these drugs have side effects, such as nausea, sleeplessness, or mood swings. Your doctor or pharmacist will provide details on possible side effects, and your doctor will monitor you closely if you are taking one of these drugs.

Nicotine replacement therapies and non-nicotine medications work best when used in conjunction with a behavioral counseling program. These medications can help reduce your urge to smoke, but quitting is still up to you. You must commit to changing the habits that trigger and maintain your smoking. While making a lifestyle change isn't easy, this is one change that could save your life. ■

– S. Moreau

FOR MORE INFORMATION

For information about smoking cessation programs:

- *Ask your physician*
- *Call 713-792-QUIT*
- *Visit www.mdanderson.org/quitnow*

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IN BRIEF

Vaccine Explored to Reduce Risk of HER2-Positive Breast Cancer Recurrence

Adjuvant immunotherapy with the GP2 vaccine shows promise in preventing disease recurrence in patients with high-risk human epidermal growth factor receptor 2 (HER2)–positive breast cancer, especially in patients previously treated with trastuzumab.

GP2 is a HER2-derived immunogenic peptide that binds to cells that are positive for human leukocyte antigen (HLA)-A2. The vaccine is a mixture of GP2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) as an immunoadjuvant.

A phase II trial of the vaccine was conducted at The University of Texas MD Anderson Cancer Center and other institutions. The trial enrolled HLA-A2–positive patients who were cancer free after standard treatment for breast cancer; all patients had cancer that expressed the HER2 protein. The patients were at high risk for recurrence because they had lymph node–positive disease or other factors, such as high levels of HER2 expression.

Patients in the study were randomly assigned to receive adjuvant therapy with the GP2–GM-CSF vaccine or GM-CSF only. Treatment was given in an initial series of six monthly subcutaneous injections followed by four booster shots administered at 6-month intervals.

Eighty-nine patients received the GP2–GM-CSF vaccine, and 91 patients received GM-CSF only. At a median follow-up of 34 months (range, 1–60 months), disease-free survival rates were 94% and 85% for patients receiving the entire course of treatment with the GP2–GM-CSF vaccine and GM-CSF only, respectively ($P = 0.17$). Patients in both arms of the trial continue to be followed up for evidence of disease recurrence.

Although the difference in disease-free survival was not statistically significant, the researchers were encouraged by the finding that the 48 patients whose tumors had high levels of HER2 expression and who received the GP2–GM-CSF vaccine had a 100% disease-free survival rate.

The reason no recurrences occurred in patients whose tumors overexpressed HER2 may be that these patients received trastuzumab as part of standard therapy. According to Elizabeth Mittendorf, M.D., Ph.D., an associate professor in the Department of Surgical Oncology, trastuzumab may act as a primer for the vaccine. Trastuzumab stimulates CD4-positive T cells and initiates an antibody response. Thus, trastuzumab may act synergistically with the GP2–GM-CSF vaccine. MD Anderson is now testing this combination of immunotherapies in other clinical trials.

"We are investigating ways to prevent cancer recurrence by stimulating the immune system," Dr. Mittendorf said. She and her colleagues presented the findings of their analysis in September at the American Society of Clinical Oncology's 2014 Breast Cancer Symposium. ■

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