Understanding and Managing Multiple Endocrine Neoplasia Syndromes

By Zach Bohannan

Endocrine tumors caused by multiple endocrine neoplasia syndromes (MEN) pose a dual threat—both from the tumors' potential for growth or metastasis and from their hormonal secretions.

Although endocrine tumors make up only about 3% of newly reported cancer cases, some individuals develop many of these tumors over the course of their lives because of rare genetic conditions such as MEN.

A number of genetic syndromes can cause the development of multiple endocrine tumors. The ones seen most often are broadly classified as MEN type 1 (MEN1) and MEN type 2 (MEN2). Each is characterized by mutation of a specific gene and a specific distribution of tumors.

MEN2

MEN2 is actually a set of syndromes caused by mutations in the RET proto-oncogene, which encodes a receptor tyrosine kinase. These mutations activate the receptor and cause cellular hyperplasia, tumor formation, and medullary thyroid cancer. Because of the nature of the mutations and RET’s location on a non-sex chromosome, MEN2 is inherited in an autosomal dominant fashion.

Although the mutant gene is present in every cell in the patient’s body, only a subset of the tissues in which the gene is expressed develop tumors or grow abnormally. “MEN2 mostly
causes neoplasia in a few tissues, such as the thyroid, parathyroid, and adrenal glands, but why these tissues alone are affected remains unclear,” said Gilbert Cote, Ph.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center.

Because MEN2 is a genetic disorder, researchers have been able to develop a variety of tools to study the disease. The best source of information is harvested tumor samples. Dr. Cote said, “Most of our research is derived from the use of patient tumor tissues or primary cell lines.” A few MEN2 mouse models have been developed, but the associated traits in mice may differ from those in humans. One reason may be differences in the organisms’ life spans: MEN2 patients first develop thyroid tumors and then parathyroid and adrenal tumors; mice may not live long enough to develop tumors in all these sites.

MEN2 is divided into three clinical subtypes: MEN2a, MEN2b, and familial medullary thyroid carcinoma. The graph on page 1 shows the tumors associated with each subtype.

**Thyroid tumors**

The development of medullary thyroid cancer is often the first sign that a patient may have MEN2. Furthermore, nearly all MEN2 patients experience thyroid C-cell hyperplasia, even if they lack identifiable tumors, and most will develop thyroid cancer if their thyroid gland is not surgically removed at a relatively young age. Unlike most sporadic, nonhereditary thyroid cancers—which have a papillary or follicular histology—MEN2-associated thyroid tumors are derived from parafollicular C cells and almost always overproduce the hormone calcitonin. When produced in large amounts, calcitonin can cause flushing episodes and diarrhea.

A more detailed article about the treatment of thyroid tumors can be found in the July 2010 issue of OncoLog.

**Pheochromocytoma**

In the general population, most adrenal tumors are nonsecretory and are detected only incidentally. These tumors may require follow-up imaging studies and hormonal assessment, but many are benign neoplasia. However, MEN2 patients have about a 50% risk of developing pheochromocytomas, adrenal tumors that are usually benign but secrete epinephrine or norepinephrine.

The excess epinephrine and norepinephrine produced by pheochromocytomas can cause weight loss, anxiety, headaches, palpitations, sweating, and dangerously high blood pressure.

**Treatment for MEN2**

Surgery is currently the most common treatment for MEN2-related tumors. Several pharmacological agents are available to treat the various hormonal secretions produced by MEN2 tumors, but these agents generally do not affect the size or growth of the tumors themselves.

Since thyroid tumors are often the first malignancies to develop with MEN2, children identified as having the genetic disorder may undergo prophylactic thyroidectomies to prevent the development and spread of medullary thyroid cancer. Prophylactic thyroidectomies may be recommended as early as within the first year of life for children with MEN2b and by 5 years of age for those with a less aggressive form of MEN2a.

Prophylactic thyroidectomies may be deferred for children with lower-risk RET mutations until there is clinical evidence of C-cell hyperplasia or medullary thyroid cancer based on annual ultrasonography and measurement of serum calcitonin levels.

Lifelong thyroid hormone replacement is required after thyroidectomy, but the long-term effects of hypothyroidism, particularly if uncontrolled, remain largely unknown, as do oncological outcomes after prophylactic thyroidectomy.

New drugs are also available to manage thyroid cancer in patients for whom surgery is not an option. Steven Waguespack, M.D., an associate professor in the Department of Endocrine Neoplasia and Hormonal Disorders, said, “There is a new drug, vandetanib, that specifically targets the RET gene and shows promise for treating MEN2 patients with advanced medullary thyroid cancer when surgery may not be feasible.” Vandetanib recently was approved by the U.S. Food and Drug Administration for the treatment of such patients.

Pheochromocytomas are managed less aggressively than thyroid tumors in MEN2 patients because the adrenal tumors are rarely malignant. Usually, when a patient with MEN2 develops a pheochromocytoma, only the affected adrenal gland is removed. Jeffrey Lee, M.D., the chair of and a professor in the Department of Surgical Oncology, said, “Thankfully, patients can have one adrenal gland removed and still live a normal life.”

Eventually, many MEN2 patients may need to have both adrenal glands removed and receive replacement hormones, but delaying this treatment as long as possible (or removing just the part of the adrenal gland that contains tumor) allows patients to maintain a normal lifestyle for as long as possible. Most pheochromocytomas can now be removed using a minimally invasive approach, such as a retroperitoneoscopic adrenalectomy, allowing for more rapid recovery.

Although surgery remains the gold standard for treating MEN2 tumors, for patients who present with metastatic cancer there is no cure. Research on the molecular mechanism of MEN2 has led to some promising treatment options that attempt to target the activated RET tyrosine kinase receptor. A new class of agents known as tyrosine kinase inhibitors is being studied in clinical trials for the treatment of thyroid cancers. Among these drugs is the recently approved vandetanib. Studies conducted at MD Anderson and other cancer centers suggest this class of drugs may be effective at combating the thyroid tumors caused by MEN2.

**MEN1**

Although the disorders share a name, MEN1 and MEN2 are very dif-
ferent. For instance, parathyroid tumors are almost always present in patients with MEN1 but are relatively uncommon in patients with MEN2. MEN1 also causes pituitary adenomas and pancreaticoduodenal neuroendocrine tumors (PDNETs).

MEN1 is caused by a loss of function in the MEN1 gene. This gene is thought to play a role in chromatin maintenance, but the gene is not yet well understood. MEN1 is inherited dominantly, like MEN2.

Interestingly, the mutant MEN1 gene is also expressed in a wide variety of tissues other than those affected by MEN1. The disorder may depend on trigger events that are specific to the tissues it affects. Dr. Cote said, "It may be that the tissues affected by MEN1 are more likely to experience mutations or loss of the normal copy of the MEN1 gene, but this is an area of active investigation."

**Parathyroid tumors**

Parathyroid hyperplasia causes hyperparathyroidism in patients with MEN. A more detailed article on the symptoms and treatment of parathyroid tumors can be found in the March 2010 issue of OncolLog.

**Pituitary adenomas**

Like other MEN-associated tumors, pituitary adenomas resulting from MEN1 are usually benign, but they can secrete a variety of hormones and be more locally aggressive. Adrenocorticotropic hormone–producing pituitary tumors can stimulate the adrenal glands to secrete excess adrenal hormones and, therefore, cause many of the same symptoms as secretory adrenal tumors. Similarly, tumors that produce thyroid-stimulating hormone can mimic the effects of hyperthyroidism. Pituitary adenomas can also secrete growth hormone, which can cause gigantism or acromegaly, or prolactin, which can cause reduced sex hormone levels.

Despite their often slow-growing nature, pituitary adenomas can also pose a threat because of their location. The pituitary gland is confined in a small space, and even a minimal level of tumor growth can cause drastic symptoms. Notably, the tumors can cause pressure on—and damage to—the optic nerve or the surrounding healthy pituitary tissue.

**PDNETs**

Like other endocrine tumors, PDNETs can secrete hormones associated with their tissue of origin: the pancreatic islet cells. In fact, PDNETs are often classified according to their secretions, which can produce a variety of symptoms. For example, gastrin-secreting tumors (gastrinomas) can cause ulcers, and insulinomas can cause drastic hypoglycemia.

"These tumors present two distinct difficulties for treatment," said James Yao, M.D., an associate professor in the Department of Gastrointestinal Medical Oncology. "On the one hand, you must manage the general oncological symptoms; but on the other hand, you must also manage the severe symptoms associated with any hormones the tumor produces."

**Managing MEN1**

Like patients with MEN2, patients with MEN1 are regularly monitored for tumor development. They typically undergo yearly biochemical screenings and interval abdominal computed tomography or magnetic resonance imaging to detect any developing pituitary or pancreatic tumors. As is the case for MEN2, surgery is often the best option for most MEN1-derived tumors. Unfortunately, some of the tissues commonly affected by MEN1 tumors are more difficult to operate on than those affected by MEN2 tumors.

Although the parathyroid glands are important for calcium homeostasis, typically all glands in patients with MEN1 are affected by parathyroid hyperplasia. As Nancy Perrier, M.D., a professor in the Department of Surgical Oncology, explained, "MEN1-associated hyperparathyroidism occurs at an earlier age than its sporadic counterpart, usually affecting patients by the third or fourth decade of life. Because it is the result of a genetic mutation of all parathyroid tissue, the syndrome is characterized by multiple gland involvement. If not treated as such, recurrent or persistent disease is common. The surgical procedure should include resection of the majority of parathyroid glands—usually a three-and-a-half-gland resection. Concomitant cervical thymectomy is advised to remove supernumerary glands and to decrease the risk of malignant thymic carcinoids."

Pituitary tumors usually are not treated until they become clinically evident. Pituitary tumors’ hormonal secretions can often be managed pharmacologically, but surgery typically is undertaken for pituitary tumors whose symptoms cannot be managed pharmacologically.

Recent advances have made hormonal secretion management easier. The MEN1-associated tumors most affected by new pharmaceutical products are PDNETs. Previously, PDNET patients often died because of the secondary symptoms associated with hormonal secretions. However, modern drugs, like proton pump inhibitors that can be used to treat severe diarrhea, have made these symptoms more manageable and allowed doctors to focus on the treatment of on-
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cological symptoms. The only exception is hypoglycemia caused by insulin-producing tumors, which remains relatively difficult to treat medically.

The primary treatment for PDNETs is surgical resection. “Surgical resection for MEN1-associated gastrinomas is associated with a durable return to normal gastrin levels,” said Elizabeth Grubbs, M.D., an assistant professor in the Department of Surgical Oncology. Unfortunately, in PDNETs there is a high chance of tumor recurrence even after complete surgical resection. In addition, unlike most of the other tumors caused by the MEN disorders, pancreatic tumors can be difficult to treat surgically, and the pancreas has no “back-up” glands to compensate for its resection. However, new research is offering some promising chemotherapeutic options for patients with advanced pancreatic tumors from MEN1 or other causes.

A multicenter clinical trial recently compared the effectiveness of everolimus, a mammalian target of rapamycin inhibitor, to that of placebo in patients with unresectable or metastatic pancreatic neuroendocrine tumors. The researchers found that the 18-month progression-free survival rate was significantly higher in the everolimus group (34%) than in the placebo group (9%). Dr. Yao, the principal investigator for the trial at MD Anderson, said, “We found that everolimus is actually very good at controlling insulin secretion from these tumors as well.”

Genetic testing

Since the MEN syndromes are caused by mutations, there is a growing role for genetic testing in their treatment. Many MEN patients know of their family history, but others undergo genetic testing after they develop a characteristic disease. Thereasa Rich, a genetic counselor with MD Anderson’s MEN Specialty Clinic, said, “If we see early medullary thyroid carcinoma, for instance, we often recommend genetic testing, since this disease is very rare in younger patients without MEN mutations.”

This testing also helps inform treatment options, especially for MEN2. However, the field of MEN-specific treatment is still in its infancy. The MEN Specialty Clinic at MD Anderson is a new interdisciplinary venture that integrates the results of genetic testing and treatment. Dr. Grubbs and Ms. Rich have recently received a grant to characterize in more detail the various mutations that cause MEN2. Ms. Rich said, “Many RET mutations have different effects. For instance, the RET918 mutation causes very aggressive medullary thyroid tumors, whereas some other mutations may not cause such aggressive disease and could be treated later.” Using this knowledge, endocrinologists, surgeons, and genetic counselors may be able to personalize treatment for each patient’s specific mutation.

A way forward

Currently, management of the MEN disorders is often limited to treatments for each tumor that arises. And because of the rarity of the syndromes, individual institutions generally have not seen enough MEN patients to make clinical trials feasible. However, because of the rapid increase in national and interdisciplinary collaboration, clinical trials and integrated treatment strategies are starting to be available for these and other rare disorders.

“This increased collaboration is rapidly leading to new treatments for these cancers,” Dr. Yao said, “It’s a very productive time for the treatment of rare diseases.”

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Two-Stage Resection Regimens Lengthen Survival with Liver Metastases

By Bryan Tutt

New surgical techniques and new chemotherapy drugs have pushed up the median survival times for patients with liver metastases from colorectal cancer since the 1990s.

Patients with colorectal cancer metastases involving both lobes of the liver were once considered poor candidates for surgery because removing all the metastases in a single hepatectomy would not leave enough healthy liver tissue for the patient to survive. Two-stage liver resection—in which a limited liver resection is performed to remove some metastases and to help physicians determine whether a second, more extensive resection would benefit the patient—was widely adopted in the late 1990s, making surgery possible for more patients.

Because the surgery is usually done only in patients who have responded to chemotherapy—and because several new and potent chemotherapy drugs were approved for the treatment of colorectal cancer in the 1990s and early 2000s—some physicians have questioned whether the survival benefits of two-stage resection are the result of selection bias.

Advances in chemotherapy

Patients with colorectal cancer— with or without metastatic disease—typically are treated by resection of the primary colorectal tumor followed by chemotherapy. The chemotherapy regimen for these patients has evolved rapidly in recent years. Most patients with
colorectal cancer were treated with 5-fluorouracil and leucovorin until 1994, when irinotecan was approved by the U.S. Food and Drug Administration and added to the regimen. In 1998, leucovorin replaced levasimole in the regimen, and in 2004 oxaliplatin replaced irinotecan to create the FOLFOX regimen that is now the standard chemotherapy for patients with colorectal cancer. Since 2004, monoclonal antibodies such as bevacizumab, cetuximab, or panitumumab have been added to the regimen for many patients with colorectal cancer. The addition of these monoclonal antibodies to the regimen has been shown to prolong survival in patients with colorectal cancer liver metastases and to reduce the size of the metastases.

“Because response to chemotherapy is the best predictor of outcome in patients with colorectal liver metastases, it is logical to consider response to treatment when selecting candidates for surgery,” said Jean-Nicolas Vauthey, M.D., a professor in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center.

Selecting patients for surgery

During their course of chemotherapy, patients with colorectal cancer liver metastases who are candidates for two-stage liver resection are regularly evaluated by computed tomography (CT) to assess the response of the metastases to treatment. Because chemotherapy can cause liver damage, surgeons and medical oncologists consider it preferable to begin the two-stage resection after 2–3 months of treatment; 6 months of chemotherapy can potentially cause enough liver damage to preclude surgery. Chemotherapy is resumed after the patient has recovered from surgery.

“We’re continually adjusting our practices to optimize outcomes for these patients,” said Scott Kopetz, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology. “We want to administer just the right regimen of chemotherapy for just the right duration to shrink the tumors enough to make surgery feasible without causing toxicity to the liver.”

In addition to shrinking the tumors, which for some patients is necessary before two-stage resection is possible, chemotherapy helps physicians determine whether a patient will benefit from the surgery. “We know that patients whose disease progresses during chemotherapy will have bad outcomes,” Dr. Vauthey said. “For these patients, resection of the metastases is not worth the morbidity of surgery.”

Patients are selected for the first stage of surgery on the basis of the response of their metastases to chemotherapy as indicated by CT. Signs of a response include shrinkage of the metastases and changes in the tumors’ appearance. Dr. Vauthey said that a homogenous, cyst-like appearance on CT can indicate a response to chemotherapy even if the size of a metastasis has not changed. Patients considered to have stable disease or a response to therapy are likely to be good candidates for resection of their liver metastases.

Surgeons used to consider patients with more than four metastases in the liver to be poor candidates for resection, but Dr. Vauthey said the number of metastases to be resected is now considered less important than the response to chemotherapy and the amount of cancer-free liver that can be preserved.

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A Patient’s Perspective

[Name] was diagnosed with colorectal cancer in 1998 at [Hospital]. While recovering from the resection of his primary tumor at a hospital in [Location], he received the bad news that the cancer had metastasized to his liver. He was treated with a chemotherapy regimen of 5-fluorouracil and leucovorin and referred to Dr. Jean-Nicolas Vauthey for a two-stage liver resection in [Location]. A portal vein embolization was used to increase the amount of the healthy liver tissue before the second stage of surgery.

After recovering from surgery, [Name] was able to return to his normal activities, including competitive long-distance running. For the past 12 years, he has had no recurrence of his colorectal cancer, although he was treated for an [Indicate condition] He is examined twice a year at a cancer center near his current home in [Location], but otherwise has a more active lifestyle than many people who have never had cancer.

Mr. [Name] continues to work full-time in a job that requires international travel, and he still runs marathons. “I pretty much live a normal life,” he said.
Patients are likely to be selected to undergo two-stage resection if their metastases are located such that 20% or more of the liver will be preserved after the second stage. Metastases in other sites do not necessarily preclude the resection of liver metastases.

According to Dr. Kopetz, about 1 in 5 patients with colorectal cancer liver metastases could be candidates for either a one-stage or two-stage resection, but only 1 in 20 actually undergoes a resection. To ensure that surgery is available to all patients who might benefit from it, surgeons at MD Anderson are typically consulted before patients with colorectal cancer liver metastases begin chemotherapy. “Surgery and chemotherapy are two modalities in which we’ve seen fairly significant advances independently, but the best outcomes occur when these two are integrated,” Dr. Kopetz said.

Two-stage resection

The first stage of surgery for colorectal cancer liver metastases is a limited resection of the metastases in the less affected side of the liver (usually the left side). Following this relatively minor procedure, a multidisciplinary team of physicians evaluate several criteria to determine whether they should attempt the second stage of surgery, an extended resection of the more-involved side of the liver.

The most important of these criteria is the resected tumors’ response to chemotherapy, which is determined by a pathological examination. Patients whose metastases do not show substantial response based on a decrease of viable cancer cells are unlikely to benefit from further surgery.

Another important consideration is whether the patient’s liver will be able to recover from a second surgery. To determine this and to increase the size of the healthy liver that will remain after the second surgery, a radiologist performs a portal vein embolization 2 weeks after the first surgery. Three-dimensional CT scans taken before and 3 weeks after the portal vein embolization are used to calculate the degree of hypertrophy. “We don’t know exactly why, but some people’s livers regenerate better than others’, ” Dr. Vauthey said. “Portal vein embolization provides an in vivo test telling us whether the patient is likely to have hepatic insufficiency after the second surgery.”

In addition to poor response to chemotherapy or lack of hypertrophy, complications from the first surgery or disease progression after the first surgery may prevent a patient from undergoing the second surgery. According to Dr. Vauthey, nearly a third of patients who undergo the first stage do not undergo the second stage.

Prolonged survival has been documented among patients who undergo two-stage liver resection. In fact, chemotherapy plus two-stage resection is considered curative for a small subset of patients. But the benefits of chemotherapy plus surgery compared with chemotherapy alone for colorectal cancer liver metastases have only recently been studied.

Solving the mystery

To determine whether two-stage liver resection was independently associated with survival in patients with colorectal cancer liver metastases, Drs. Vauthey and Kopetz, along with other researchers at MD Anderson, conducted a retrospective study comparing the outcomes of patients who underwent the surgery and chemotherapy to those of patients who received chemotherapy only.

The researchers reviewed the records of 65 patients who had undergone chemotherapy plus at least the first stage of two-stage liver resection and 62 patients who had received chemotherapy only between June 2002 and February 2010. The two groups were similar in terms of their performance status, absence of extrahepatic metastases, extent of hepatic metastases on pretreatment imaging, and objective response to first-line chemotherapy regimens that included irinotecan or oxaliplatin with or without bevacizumab or cetuximab.

The results of the study were recently reported in the Journal of Clinical Oncology. The 3- and 5-year overall survival rates were 67% and 51%, respectively, for patients who underwent at least the first stage of two-stage resection versus 41% and 15%, respectively, for patients who underwent chemotherapy only. The 3- and 5-year overall survival rates were significantly higher (84% and 64%, respectively) among patients who underwent the second stage of resection than among those who underwent the first stage only.

While these data support the survival benefits of surgery over chemotherapy only, they also indicated that newer chemotherapy regimens confer a greater survival benefit than previous regimens. In fact, the MD Anderson authors noted that the 5-year overall survival rate of 15% for patients receiving chemotherapy only was the highest reported rate for patients whose colorectal cancer liver metastases were treated nonsurgically. A previous study found that patients diagnosed with colorectal cancer liver metastases between 1990 and 1997 had a 5-year overall survival rate of only 9%. Dr. Vauthey said the recently published data are encouraging because they demonstrate that advances in treatment have been followed by improved patient survival rates.

“To answer the question of whether the surgical procedure or the drugs are responsible for the improved survival durations for these patients—the answer is both,” Dr. Vauthey said.

“Portal vein embolization provides an in vivo test telling us whether the patient is likely to have hepatic insufficiency after the second surgery.”

– Dr. Jean-Nicolas Vauthey

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Saving a Life by Donating Stem Cells

Facts about stem cell transplants

Stem cell transplantation can be a life-saving treatment for many patients affected by various diseases. Leukemia, for example, attacks patients' bone marrow, which produces stem cells. Stem cells can mature into any of the types of blood cells needed to transport oxygen and fight infection in the body. Fortunately, stem cell transplantation can restore the ability of the bone marrow to produce blood cells. Among the other diseases that may be treated with stem cell transplantation are lymphoma, multiple myeloma, and sickle cell anemia.

Types of transplants

There are three types of stem cell transplants: those in which patients receive their own previously removed stem cells, those in which patients receive stem cells from a relative, and those in which patients receive stem cells from a volunteer donor who is not related. Receiving cells that closely match a patient's own stem cells reduces the risk that the patient's immune system will reject the transplanted cells. Close relatives are more likely to have stem cells that match the transplant recipient's stem cells. Patients who don't have a close relative with matching stem cells must hope that a match will be found through volunteer donor registries.

Stem cells can be obtained from a donor's bone marrow or from the blood circulating in the body (called peripheral blood). Both methods of donation are very safe but can cause discomfort and side effects. Stem cells can also be donated from umbilical cord blood after a baby is born.

Donating stem cells

During bone marrow donation, the donor is placed under anesthesia at a hospital, and a needle is inserted into the hip bone to remove some bone marrow. The donated bone marrow is filtered to remove red blood cells and tiny pieces of bone. The bone marrow is then either given to a transplant recipient or frozen for future use. The donor then recovers in the hospital for a few hours or overnight. After bone marrow donation, the donor may have lower back pain, fatigue, and stiffness for a few days. Most bone marrow donors completely recover within 3 weeks as the body forms new stem cells.

Peripheral blood stem cell donation has two steps. First, for 5 days before the donation, the donor receives injections of a drug called filgrastim. This drug increases the number of stem cells in the blood. The second step is much like a plasma donation. Blood is removed through a needle inserted in the donor's arm, the stem cells are filtered from the blood, and the blood is returned to the donor in the other arm. The donation process takes just a few hours.

Before donating peripheral blood stem cells, the donor may have a headache and bone and muscle aches as a side effect of filgrastim. During the donation, the donor may feel a tingling sensation around the mouth, fingers, and toes. Most peripheral blood stem cell donors recover fully within 2 weeks.

Donating cord blood

Pregnant women can donate their baby's umbilical cord blood, which is rich in stem cells. The blood is collected from the placenta and umbilical cord just after the baby is born. The blood is then tested to see if it contains enough stem cells for use in a transplant. If the blood is suitable for transplantation, it is frozen, listed with the National Marrow Donor Program, and stored until a match is found for a transplant recipient. The donation poses no risk to the mother or baby.

Becoming a donor

To donate umbilical cord blood, you should contact a cord blood bank in your area at least 6 weeks before your due date. The National Marrow Donor Program provides a list of cord blood banks and collaborating hospitals, as well as options for women who wish to donate but are not delivering at such hospitals. You can become a bone marrow or peripheral blood stem cell donor by joining the National Marrow Donor Program's Be The Match Registry. When you join, you can go to a donor center in your area where a DNA sample will be taken by either a blood test or a cheek swab, or you can complete the registration process online and have a DNA test kit sent to your home. In some cases, there is a nominal fee to join the registry, but the costs of the donation itself are typically paid by the transplant recipient's medical insurance.

Stem cell donation involves some inconvenience and discomfort, but saving a life makes it worth the effort.

M. Wade

FOR MORE INFORMATION
- Talk to your physician
- Call the MD Anderson Stem Cell Transplantation and Cellular Therapy Center at 713-792-6100
- Call the MD Anderson Cord Blood Bank at 713-563-8000 or 866-869-5111
- Visit the National Marrow Donor Program at www.marrow.org
Study Reveals How EZH2 Protein Promotes Breast Tumor-Initiating Cell Growth

Researchers from MD Anderson recently discovered the mechanism by which the EZH2 protein, which is essential to normal stem cell renewal, also promotes an increase in the number of breast tumor-initiating cells. The researchers also found that two drugs block this mechanism and the subsequent increase in the number of breast tumor-initiating cells.

Overexpression of the EZH2 protein had previously been linked to breast cancer progression, but the molecular details of that connection were unknown, according to Mien-Chie Hung, Ph.D., chair of and a professor in the Department of Molecular and Cellular Oncology and the senior author of the study’s report in the January 18 issue of Cancer Cell.

The researchers found that a hypoxic tumor microenvironment can initiate a molecular cascade that fosters the self-renewal, survival, and growth of breast tumor-initiating cells. First, the lack of oxygen stimulates the hypoxia-inducible factor 1α protein, which in turn binds to the promoter region of the EZH2 gene and causes EZH2 overexpression. The abundant EZH2 then slows the production of RAD51, an important tumor suppressor protein involved in DNA damage repair. As DNA damage and chromosomal aberrations mount in the absence of RAD51, the production of protein kinase RAF1 is amplified, triggering the MEK-ERK-β-catenin signaling pathway, which in turn promotes the increase of breast tumor-initiating cells and cancer progression.

To determine which drugs might block this cascade, the team tested five antitumor drugs—sorafenib, imatinib, lapatinib, paclitaxel, and the small molecule RITA (reactivation of p53 and induction of tumor cell apoptosis)—in human primary breast cancer cells and in a xenograft mouse model of human tumor cells. Sorafenib, an inhibitor or RAF1 and other targets, eliminated more breast tumor-initiating cells and blocked tumor formation more effectively than the other four drugs.

To test whether sorafenib’s effectiveness was the result of its inhibiting RAF1 or a different target, the researchers then investigated AZD6244, an experimental drug that specifically inhibits the MEK-ERK kinase cascade launched by RAF1. AZD6244 eliminated EZH2-promoted breast tumor-initiating cells and blocked the formation of xenograft tumors and mammospheres, cell spheroids originated from self-renewing tumor-initiating cells.

Dr. Hung said the drugs’ inhibition of the breast tumor-initiating cells revealed the prevention of breast cancer progression as a previously unidentified therapeutic effect for RAF1-ERK inhibitors.