New test accurately predicts which family members will develop thyroid cancer

Genetic testing: a new paradigm for medullary thyroid carcinoma

When Cathy Parker was ten years old, her life changed forever. She lost her mother to pheochromocytoma, a neoplastic adrenal disorder known to occur as part of a clinical syndrome called multiple endocrine neoplasia type 2, or MEN 2, which also encompasses parathyroid neoplasia and medullary thyroid carcinoma, or MTC. While struggling with the loss of her mother, Cathy learned that the syndrome is hereditary and that she stood a 50 percent chance of having inherited it herself.

Pheochromocytoma and MTC are the most threatening of these diseases, said Robert F. Gagel, M.D., chief of the Endocrine Section of The University of Texas M. D. Anderson Cancer Center. Medullary thyroid carcinoma develops in over 90% of individuals who inherit MEN 2, and the death rate from MTC that has spread to other parts of the body is 15 to 25 percent. Pheochromocytoma may cause high blood pressure, heart irregularities, or even death if not treated. The parathyroid tumors are generally benign but may cause blood calcium levels to be elevated.

Screening tests not definitive

After her mother’s death, Cathy (not her real name) was checked annually for signs of these three disorders, as were individuals from many other families known or believed to be affected by MEN 2. This screening included a pentagastrin or a combined pentagastrin/calcium test, which detects early abnormal elevations in calcitonin level, a sign of MTC; serum or urine catecholamine measurements to detect early adrenal medullary abnormalities, which often accompany MTC; and serum calcium measurements to detect parathyroid abnormalities. Although these tests are useful in identifying these tumors at early, treatable stages, they are far from definitive: the pentagastrin test, for example, has a high false-positive rate, meaning that some patients who did not actually have MTC have been treated unnecessarily.

For patients with MTC, that treatment means surgery, complete removal of the thyroid gland. The only outward sign of this surgery is a small scar on the neck that fades with time; regular, lifelong hormone replacement therapy allows most patients to live a normal life. One to three percent of patients who undergo this surgery have a low blood level of calcium, necessitating calcium and vitamin D supplementation, or develop hoarseness, suggesting that the procedure can damage the vocal cords.

Cathy’s diagnosis came when she was 18. For the first time, the screening tests detected an elevated calcitonin level, indicating MTC. Her thyroid gland was removed shortly after, and she was believed cured. Meanwhile, however, endocrinologists treating patients with MTC found evidence of metastasis in children as young as six years old. They began to realize that, for many patients, even adolescence was too late for the surgery, and that the thyroid should be removed much earlier, preferably in its hyperplastic or precancerous state, to prevent metastasis. They were in a quandary: earlier surgery was clearly indicated, yet they could not operate until they had clinical evidence of disease, an elevated calcitonin level. A new test that would detect the disease earlier and more accurately was needed. Researchers at M. D. Anderson and other institutions believed that the best hope for individuals with the hereditary form of MTC was a test that could detect the genetic abnormality that causes the disease.

continued on page 2
Cathy grew up, married, had children. At one of her regular check-ups—standard for people who have been treated for cancer—Cathy was found to again have an elevated calcitonin level, a sign of metastatic disease. She has no signs of the metastasis, however, and without further treatment remains well. Her younger brother, who also had a thyroidectomy as an adolescent and was later found to have metastatic disease, is not so lucky. He has severe symptoms and is being aggressively treated.

Genetic analysis key to early detection

While Cathy was raising her children, researchers at M. D. Anderson and other institutions were conducting the painstaking genetic research that would allow development of a test that could detect the genetic abnormality long before the disease was detectable clinically. Wanting to spare her children her brother’s fate, Cathy and her family helped by supplying blood samples on request to Gagel and his colleague, Gilbert Cote, Ph.D., of the Endocrine Section. Eventually the abnormality was discovered to be a DNA mutation in a gene called RET.

When, in 1993, a blood test for this mutation finally became available, Cathy’s children were nine and eleven years old and neither had shown any signs of MEN 2. The Parkers decided to have their children tested immediately by the new, more sensitive test. Said Cathy, “We welcomed the opportunity to know for sure. If either of the children were affected, we wanted to know as soon as possible so we could take immediate action.” Gagel affirmed their choice: “We now can determine with nearly 100 percent accuracy whether a child with an affected parent has the RET mutation. We also know that 90 to 95 percent of children who have the mutation will go on to develop MTC. This gives us more accurate information for clinical decision-making and is a logical extension of earlier efforts to detect the tumor before it spreads.”

All the same, when the Parkers learned that the younger child, a boy, was affected, “it hit like a ton of bricks,” recalled Cathy. “It worked as it was supposed to: one child had it, one didn’t,” she said, referring to the autosomal pattern of inheritance that gives each child a 50-50 chance of inheriting the mutation that causes the disease. The Parkers then faced the choice of whether to have their son’s thyroid removed. Gagel and his surgeon colleagues recommended thyroidectomy. They believe that thyroidectomy is the best choice for patients who carry the mutation, and they are glad to be able to finally offer a test that can give an early and highly accurate prediction of an individual’s risk of developing MTC. The Parkers chose thyroidectomy for their son.

To test or not to test

Some parents choose not to have themselves or their children tested even though family members have had MTC. Others will have the test but will choose to not treat family members who test positive. Gagel speculated that these families probably believe that the disease is not that serious because no family member has died of it in recent memory. He emphasized, however, that MTC is very unpredictable and could suddenly turn deadly in the next generation. He and his colleagues at M. D. Anderson always take the time to help families understand the risk. They discuss with affected individuals and their family members the advantages and disadvantages of the test and the surgery. A pamphlet describing the test and the treatment is provided to all families.

Gagel noted that studies going on at M. D. Anderson and other institutions will allow even more precise targeting of who should have the test and who does not need to. “We expect that future discoveries will allow us to predict more accurately who will get the disease and how the tumor will behave. This knowledge should also allow us to refine our treatment strategies.” Gagel and Cote have worked closely with Maher Albitar, M.D., director of the Molecular Diagnostics Laboratory in the Division of Laboratory Medicine, to make the test available to clinicians.

A paradigm for genetic testing

Gagel sees the test for the RET mutation as a model for understanding not only the medical and surgical implications of genetic tests that accurately predict cancer development, but also the ethical, psychosocial, and financial implications. The development of the genetic test moved so quickly from the discovery of the mutation

continued on page 5
New trial reflects changing strategies

Adjuvant chemotherapy for breast cancer: 20 years of progress at M. D. Anderson

Today, more than two decades after it was first tested in clinical trials, adjuvant chemotherapy is widely used to reduce the risk of recurrence in patients with operable breast cancer. The term "adjuvant chemotherapy" refers to chemotherapy administered after the primary tumor has been treated by surgery or a combination of surgery and radiotherapy. By destroying micrometastases that remain after this local therapy, adjuvant chemotherapy can prevent disease recurrence, thus prolonging patients' disease-free and overall survival. Two drug regimens—CMF, a combination of cyclophosphamide, methotrexate, and 5-fluorouracil; and FAC, a combination of 5-fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide—and their variations have emerged as the most widely used adjuvant chemotherapy regimens for breast cancer patients.

Doxorubicin gives breast cancer therapy a boost

When researchers at The University of Texas M. D. Anderson Cancer Center began their clinical trials of adjuvant chemotherapy for breast cancer in 1973, they chose to study doxorubicin. At that time, several studies suggested that doxorubicin was the most effective chemotherapeutic agent against metastatic breast cancer. Over the past 21 years, the researchers have continued to focus on doxorubicin in combination regimens in the adjuvant setting. Leading their studies of doxorubicin today is Aman U. Buzdar, M.D., chief of adjuvant protocols and deputy chairman of the Department of Breast and Gynecologic Medical Oncology.

"In 1974, when we started the studies here, there was no clear evidence that any patient would be cured with adjuvant therapies," said Buzdar. "We gave the FAC combination to patients with macroscopic metastatic disease where we could see the response—for instance, to patients with lung tumors, which we could see on chest x-rays. When we gave those patients chemotherapy, about 20% of the time the cancer completely disappeared, and another 50% to 60% of the time, the cancer shrank to less than half of its original size. This was the first time we had a drug combination that worked 70% to 80% of the time.

"We moved that combination to the adjuvant setting for patients at very high risk of disease recurrence. We wanted to see whether any of these patients could be kept free of disease." Whereas most of the studies going on at the national level in the early 1970s, said Buzdar, were testing one, two, or three drugs at low doses, Buzdar and his colleagues administered the FAC combination at relatively high doses, with good results. "We were pleasantly surprised that there was a sizable fraction of patients who were free of disease beyond three, four, and even five years."

Clinical trials led to improved treatments

From 1974 to 1990, Buzdar and his colleagues carried out this first trial plus four other major clinical trials of regimens containing doxorubicin. Guided by the results from these trials, Buzdar and his colleagues have been able to design new treatments that are both more effective and less toxic than the early FAC regimen and its variants.

One of the ways the M. D. Anderson investigators sought to improve the effectiveness of the FAC combination was to alter the dose of doxorubicin. "We were trying to push the dose of chemotherapy to see whether we could further reduce the risk of recurrence," recalled Buzdar. "At doses above 60 mg/m^2, we've found that there is not much therapeutic gain, but the toxicity is substantial."

In the early 1970s, when the first trials of adjuvant chemotherapy were beginning across the nation, physicians were concerned about doxorubicin's long-term effects on the heart. "Long-term data, with follow-up of over 20 years, indicate that doxorubicin will cause problems in only about 1% of patients," noted Buzdar. Over a decade ago, Buzdar and his colleagues made this risk even smaller by beginning to administer the drug by continuous infusion over a three-day period. "We have found that this substantially reduces the risk of damage to the heart. Some patients still say they don't want to take the risk

continued on page 4
“I think that at every stage of disease, patients are doing better now than they were doing 20 years ago.”

of cardiac dysfunction, but the benefit, I think, outweighs the risk.”

The acute side effects associated with doxorubicin in the early trials included reversible hair loss, nausea, and vomiting. Patients still lose their hair, said Buzdar, but nausea and vomiting are no longer a problem for the huge majority of patients. “In the past few years, extremely effective antiemetics have become available. Ninety-nine percent of the time we can control the nausea and vomiting.”

One of the major unresolved questions today in the field of adjuvant chemotherapy for breast cancer is whether regimens that contain anthracyclines—doxorubicin in the United States and epirubicin, a doxorubicin analogue, in Europe—are superior to the CMF regime and its variants. According to Buzdar, the current trend in the United States is to treat high-risk patients—those with four or more disease-positive lymph nodes—with FAC-type regimens. However, for patients with fewer than four positive nodes, many physicians still favor CMF-type regimens.

At M. D. Anderson, the disease-free and overall survival rates for patients treated with doxorubicin-based regimens have been higher, in some cases significantly higher, than the rates for patients treated with CMF-type regimens at other institutions. On the basis of these results, Buzdar believes that regimens that include doxorubicin are probably superior for both high- and low-risk subgroups. He concedes, however, that there is not yet enough evidence of their superiority in patients with fewer than four positive nodes. “My bias and the bias in this institution is that even in low-risk subgroups the doxorubicin-based combinations will be superior. But to show that, and to convince the community at large, will require a lot of effort and resources. Because the risk of recurrence in this subgroup is small, we will need studies with thousands of patients to show significant survival advantages.”

New trial tests less radical surgery

Today, Buzdar and his colleagues continue to search for new treatments that will be more effective and more tolerable for patients. They have just begun a complex trial. “In this trial we are trying to answer two major questions,” said Buzdar. “Will giving a new drug before the FAC treatment further improve the odds of patients’ remaining free of cancer? Can we do less radical surgery and still achieve the same survival results in the long run?”

The trial is open to patients with $T_{2-3}, N_{0-1}, M_0$ invasive, non-inflammatory breast cancer. This means that patients with tumors up to 5 cm or even larger are eligible, as long as they have no distant metastases and their axillary lymph nodes, if affected, are not fixed together. Buzdar and his colleagues plan to enroll about 500 patients over a period of about five years.

In addition to surgery and adjuvant chemotherapy, patients in this trial will be treated with neoadjuvant chemotherapy, which is administered before surgery with the goal of shrinking the tumor and any affected lymph nodes. At the outset of the trial, patients will be randomized to receive before surgery either four cycles of FAC or four cycles of paclitaxel (Taxol), a very active drug that was first tested in clinical trials in 1983. After two cycles, patients in both groups will be evaluated, and those with evidence of progressive disease will be switched to the other group for the remaining two cycles. After the completion of all four cycles, patients will be evaluated again.

If the tumor has not shrunk significantly or if there is evidence of axillary lymph node metastases, patients will undergo mastectomy followed by four cycles of FAC and then radiotherapy. Following completion of this treatment, patients older than 50 whose tumors are estrogen-receptor positive will receive tamoxifen, an antiestrogen shown to prolong disease-free and overall survival in this subgroup, for five years.

If the tumor has shrunk significantly and there is no clinical evidence of axillary lymph node metastases, patients will be randomized to undergo either segmental mastectomy and axillary dissection or segmental mastectomy alone. In a segmental mastectomy, the breast is conserved; the surgeon removes only the tumor and, to ensure that all of the cancerous tissue is removed, a small margin of normal tissue immediately surrounding the tumor. Segmental mastectomy plus axillary lymph node dissection, on the other hand,
is a more extensive procedure and one that results in greater discomfort and disfigurement for the patient.

After surgery, patients in the two segmental mastectomy groups, like those in the mastectomy group, will receive four cycles of FAC and then radiotherapy. Again, patients older than 50 whose tumors are estrogen-receptor positive will receive tamoxifen for five years.

Buzdar hopes that follow-up data will show segmental mastectomy alone followed by irradiation of the intact lymph nodes to be as effective as segmental mastectomy with axillary dissection. "Segmental mastectomy alone is a very simple procedure," said Buzdar. "It can be done on an outpatient basis. It is much less disfiguring, and if it allows similar survival outcomes, it will be much better for patients in the long run." As for the effectiveness of the combination of FAC and paclitaxel over FAC alone, "that's another million-dollar question."

Asked what kinds of gains in survival he envisioned as a result of improved methods of adjuvant chemotherapy in the next 20 years, Buzdar was cautiously optimistic. "I wish I had a crystal ball. The thing is, we're making slow progress. We're hoping that with the new strategies we're trying now, we'll see some gains. In spite of our best efforts, a substantial proportion of patients still die of their disease. So there is a lot of room for improvement." But also room for optimism: "I think that at every stage of disease, patients are doing better now than they were doing 20 years ago. And I think we can definitely say that, based on 20 years of follow-up, there is a fraction of patients who can be cured by local therapy and adjuvant chemotherapy."

—Stephanie P. Deming

**Medullary thyroid carcinoma**

continued from page 2

that even medical professionals are not in agreement about the appropriate uses of the test. Despite the inevitable controversies surrounding genetic testing, there is good news for families affected by MEN 2. The RET mutation test is a case of a new technology improving cancer patients' chances of cure at a lower cost. Even a crude cost analysis shows that the one-time test and surgery are cheaper than the annual battery of screening tests, which are usually recommended for individuals at risk until the age of 35 years.

**Test offers a better life**

Just as the Parkers did not hesitate to have their children tested for the mutation, they knew immediately when Gagel offered thyroidectomy as a treatment option that they wanted their child to have the surgery. As Cathy said, "Why take the chance that the child will develop metastasis? I've lived without my thyroid for 20 years and it's no big deal. We believe the surgery was the best choice we could make to prevent future illness. There's no question in my mind that this test and the surgery have improved the quality of my life and of my son's."

—Kathryn L. Hale

**REFERRALS.** Physicians who have questions or would like to refer a patient may write Dr. Gagel at the Endocrine Section, Box 15, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-2840.

---

The blood test for the RET mutation is available to patients who are referred to the Endocrine Section of M. D. Anderson Cancer Center and to their families. Said Robert F. Gagel, chief of the section, "We believe that all patients with medullary thyroid carcinoma should have this test, and we have made it available in our clinical laboratory." He added, "It is important to perform this analysis on all patients with MTC, regardless of whether the disease is thought to be familial, because of the important implications for children and other family members if the test is positive."
We have organized the outpatient clinic to offer the cutting edge of developing therapies in a convenient fashion.

Bone marrow continued from page 8

high-dose chemotherapy courses and transplantations in a comfortable, cost-effective setting that could be made available to large numbers of patients, Champlin last summer pioneered the opening of the Outpatient Clinic for Bone Marrow Transplantation, giving patients who require such treatment a much greater degree of freedom than they ever had before. “Transplantation in an outpatient setting,” Champlin explained, “takes an otherwise restrictive and expensive procedure and not only makes it more tolerable for the patients but also actually permits the use of the more effective high-dose treatment strategies.”

Outpatient transplantation more flexible, less expensive

By using the Outpatient Clinic for Bone Marrow Transplantation at M. D. Anderson, patients needing autologous transplantation can bypass much of the stay in the hospital. Typically, patients achieve clinical stability about three days after they receive high-dose therapy. At this point, they can be discharged from inpatient care to the outpatient clinic. The next morning the patient can receive an autologous transplant in the outpatient clinic and return home by midday. The patient is cared for at home by a family member or a professional caregiver and returns to the clinic every day for about a month for monitoring.

Patients requiring allogeneic transplantation can also be treated in the outpatient clinic. This more complicated procedure requires that the proteins on the surfaces of the stem cells of patients be matched with those of the donors. An exact match is impossible, and the greater number of side effects in this group is due to slight mismatches in the proteins. Patients undergoing allogeneic transplantation therefore receive both their high-dose therapy and their transplant as inpatients, spending about one month in the hospital. They can then be enrolled as outpatients in the clinic and are monitored three times a week for an additional three weeks after they receive their transplant.

Support services in the outpatient clinic are as extensive as those for inpatients. A team composed of a physician, clinical nurse specialist, and clinical pharmacist is assigned to each patient. Psychological and psychiatric support is available twenty-four hours a day. M. D. Anderson is always ready to readmit the patient, and antibiotic infusions and blood transfusions are immediately available. At any time for any problem, the patient can be seen at the Ambulatory Treatment Center for Acute Care in the hospital or can call the M. D. Anderson primary physician. During the clinic’s first year of operation, no major complications or deaths occurred in outpatients.

The success of bone marrow transplantation depends on careful monitoring until the patient is clinically stable and the blood counts have returned to normal levels. The most significant risk for these immunocompromised patients, infection, is minimized by administering hematopoietic growth factors that help new marrow develop faster. The risk of infection is probably as great for a hospitalized patient as for a patient cared for at home, indicated Champlin.

The Section of Bone Marrow Transplantation has organized the outpatient clinic to offer the cutting edge of developing therapies in a convenient fashion. Champlin emphasized, “Our goal is to cure the cancer, not just to reduce the cost—the cost reduction is an added bonus.” The outpatient clinic reduces the cost of bone marrow transplantation by 50% and the length of hospital stay by 100% for autologous transplantation and 50% for allogeneic transplantation. These reductions make it realistic and practical to offer a series of supportive transplants.

Many patients eligible for outpatient transplantation

The clinic’s first patients were women with breast cancer who were suspected of having metastases. Their peripheral-blood stem cells—which allow blood counts to return to normal levels faster than bone marrow cells—were first collected and stored for future autologous transplantation. These women then underwent four monthly courses of treatment that included a two- to three-day inpatient stay for chemotherapy and a one- to four-hour outpatient stay for stem
"Transplantation in the clinic can be integrated with surgery, chemotherapy, or radiotherapy to optimize therapeutic effectiveness."

cell infusion. This series of treatments is much more effective than a single high-dose course followed by bone marrow transplantation—and in the outpatient clinic costs the same as a single inpatient treatment.

The outpatient clinic also treats patients with ovarian cancer, lymphoma, multiple myeloma, or leukemia. Transplantation in the clinic can be integrated with other treatment—surgery, chemotherapy, or radiotherapy—to optimize therapeutic effectiveness. The clinic is designed to extend the treatment that patients receive from their personal physicians; thus, referring doctors can now manage their patients’ care in concert with the Outpatient Clinic for Bone Marrow Transplantation. There is no waiting period for patients with disease that requires immediate care.

To be eligible for the outpatient program, patients must be able to reside within a 30-mile radius of M. D. Anderson during treatment and have a companion to assist in their care. Although older patients have traditionally been excluded from bone marrow transplantation, the outpatient clinic treats patients up to the age of 65 years when their medical condition is appropriate for the procedure.

Acknowledging the additional burden placed on caregivers at home as a result of outpatient treatment, Champlin said that he was pleasantly surprised by the favorable response of patients and their families. Nearly one third of the bone marrow transplantations performed by M. D. Anderson are now received by outpatients. Champlin suggested that “whereas a lengthy hospital stay compromises a patient’s sense of freedom, treatment in the outpatient clinic does not.”

—LINDA N. EPPICH

REFERRALS. Physicians who have questions or would like to refer a patient may write Dr. Champlin, Section of Bone Marrow Transplantation, Box 68, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-3611.

Oncolog on Internet

Oncolog is now available over the Internet, a worldwide network of millions of computers. Beginning with volume 39, the articles and figures of each issue of Oncolog are posted on our institution’s Gopher+ server and World Wide Web server.

Gopher clients can access Oncolog files by connecting to host utmdacc.uth.tmc.edu, port 70. World Wide Web clients can connect to http://utmdacc.uth.tmc.edu.

Other M. D. Anderson Cancer Center publications that can be viewed on one or both servers include the Research Report 1992–1993, Hereditary Colon Cancer Newsletter, and Gynecologic Oncology Newsletter. Additional cancer-related information is available on the servers, and other publications will be added soon.

We welcome your comments on Oncolog and our other publications. Electronic mail can be sent to khale@acadresources.mda.uth.tmc.edu.
Certain types of cancers respond well to very high doses of chemotherapy and radiotherapy, but these high doses cause lethal damage to the bone marrow. Bone marrow transplantation has been used for over a decade to replace these damaged blood-forming tissues, but until recently this procedure required a lengthy, expensive hospital stay to await recovery of the patient’s immune system as the transplant took effect. At the Outpatient Clinic for Bone Marrow Transplantation at The University of Texas M. D. Anderson Cancer Center, however, a patient can be infused with stem cells or bone marrow in the morning and be home in time for lunch.

Conventional transplantation impossible for some

Patients undergoing conventional transplantation remain hospitalized for the duration of the procedure. The patient first receives high-dose therapy to eradicate the tumor. In cases of autologous transplantation, that is, infusion of the patient’s own stem cells that were removed before the initiation of cancer treatment and stored at very low temperatures, the ensuing hospital stay has usually been at least one month. In cases of allogeneic transplantation, the transfer of bone marrow from a relative or unrelated donor, the patient’s immune system must be prepared to receive the donation by killing his or her own marrow with drugs to prevent rejection of the donor marrow. Because side effects are more common in these patients, allogeneic transplantation requires an even lengthier hospital stay. Further complicating matters, said Richard E. Champlin, chief of the Section of Bone Marrow Transplantation at M. D. Anderson Cancer Center, a series of high-dose chemotherapy courses is often more effective than a single treatment, necessitating a corresponding series of supportive bone marrow transplants.

The lengthy hospital stays and high costs have, in the past, made treatment protocols that require bone marrow transplantation impractical from the viewpoints of both the patient and the payer. Looking for a way to give these series of

continued on page 6