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The Good Cancer?

BY CHARLOTTE HUFF

Thyroid cancer's high survival rate masks the sometimes tricky tumor.

The first biopsy on Julia McGuire's thyroid came back negative, so the college student was regularly monitored for two years until, at one visit, the slight lump had swelled to the size of a walnut. Concerned about its recent surge in growth, her endocrinologist recommended removal, describing the surgery primarily as a precaution, although cancer was a possibility.

The 20-year-old wasn't particularly worried until her phone rang one day with the biopsy results: stage 1 papillary thyroid cancer, the most common form of the disease.

"I think it was the most traumatic moment of my life," says McGuire, now age 27. She underwent a second surgery to remove the remainder of her thyroid—a butterfly-shaped gland in the neck that regulates metabolism—and followed up with radioactive iodine to kill any lingering cancer cells. In the past seven years, she has largely moved on, with annual checkups as the only cancer reminder.

The treatment path for Rabbi Len Troupp unfolded much differently. In 1999, Troupp learned he had medullary thyroid cancer, a potentially more aggressive type, comprising fewer than 5 percent of all thyroid malignancies. Since then, Troupp has combated the cancer on several fronts, starting with the removal of his thyroid and lymph nodes in his neck and chest, followed by experimental drugs after the cancer spread to his liver and a lung, among other areas.

Nine years later, the 62-year-old appears to be benefiting from XL184, one in a cadre of investigational drug treatments for aggressive or difficult-to-treat thyroid malignancies.



Rabbi Len Troupp, at his home in New York, is receiving treatment through a clinical trial. Photo by Adrielle Rudzitis.

At least a dozen drugs, possibly as many as two dozen, are now in the clinical development pipeline to potentially treat aggressive or difficult-to-treat thyroid malignancies, according to several specialists interviewed. These drugs build on emerging insights into the roles of blood vessel growth and genetic mutations that can influence the cancer's development and progression, says David Pfister, MD, chief of the Head and Neck Medical Oncology Service at Memorial Sloan-Kettering Cancer Center in New York City.

“This is a rapidly evolving area where I think we will see a lot of research activity over the next five to 10 years,” he says.

The Big Picture

About 37,000 Americans are diagnosed annually with thyroid cancer, a malignancy that can seem relatively benign, at least where cancer is concerned.

Overall, the five-year relative survival rate for thyroid cancer is 96.9 percent or better, as long as the malignancy is diagnosed while still confined to the thyroid or nearby lymph nodes, according to the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) data.

About 90 percent of people develop either the papillary or follicular types, frequently considered treatable with surgery and radioactive iodine. Even if the malignancy can’t be knocked out completely by treatment, the cancer can often be controlled for years, in part because it can be slow-growing. But cancer survivors and treating physicians frequently wince at thyroid malignancies being described as the “good” cancer because it can throw curveballs.

The two less common types—medullary and anaplastic—can be far more aggressive and rarely respond to radioactive iodine therapy. Seemingly treatable types, such as papillary, can become less responsive over time to repeated radioactive iodine treatments. And regular checkups are crucial as recurrences can appear sometimes decades later, physicians say. In all, nearly 1,600 people die each year of thyroid cancer, according to NCI data.

Although McGuire’s tumor measured about an inch, the cancer hadn’t spread to the nearby lymph nodes. She worked treatment around her college schedule, completing surgery before her junior year and then returning home for radioactive iodine treatment over holiday break.

In retrospect, the stressful ordeal served as a wakeup call, McGuire says. She now works as an IT consultant and has assisted several cancer-related groups, including the [Thyroid Cancer Survivors’ Association](#). “I went back to school and I did better in school. I just took things more seriously.”

How much of the thyroid is removed and whether radioactive iodine is recommended depends upon a number of factors, including the tumor’s size and the extent to which it has spread beyond the thyroid itself.

Age also can play a significant role. Younger men and women—those diagnosed before age 45—are more likely to respond better to radioactive iodine treatment than older patients, says Stephanie Lee, MD, PhD, associate chief of endocrinology, diabetes, and nutrition at Boston Medical Center. The cancer is considered stage 1 in that age group, as long as it hasn’t spread to distant organs, such as the lung.

For follicular and papillary malignancies, radioactive iodine therapy can serve as a magic bullet. That’s because the thyroid naturally pulls iodine into the gland to produce hormones needed to regulate the body’s metabolism. Thus, the radioactive iodine, an isotope usually given in liquid or pill form, is easily

absorbed into the thyroid, killing cancerous cells.

View Illustration: The Radioactive Magic Bullet

Patients are typically kept isolated for 24 hours and should avoid prolonged exposure to children and pregnant women for a week or two after treatment.

Once the individual's thyroid has been removed, levothyroxine (Synthroid, Levoxyl) is prescribed to replace the body's natural thyroid hormone. (Patients must temporarily stop thyroid hormone pills prior to radioactive iodine treatment.) The dose of the synthetic hormone may need to be adjusted based on any symptoms that develop. Too much thyroid hormone can cause a rapid heart beat and weight loss. If the levels drop too low, the result can be sluggishness, weight gain, and dry skin.

Beyond Radioactive Iodine

In some malignancies, radioactive iodine isn't sufficient—or can't be used at all. The treatment is no longer recommended for medullary or anaplastic thyroid cancer. (Anaplastic comprises 1 to 2 percent of all thyroid malignancies.) Neither does radioactive iodine fully protect against recurrence.

Until recently, options beyond radioactive iodine and surgery have been limited, Pfister says. Chemotherapy has been infrequently used, other than for the most aggressive malignancies. "When we do use available chemotherapy, the response rate is disappointing," Pfister says. "That's one of the reasons there is a keen interest in these new agents."

The drugs that are emerging, nearly all in phase I or phase II clinical trials, frequently work on a variety of receptors. One common element involves inhibition of angiogenesis, or blood vessel growth to the tumor, which is believed to fuel cancer's spread.

Vascular blood vessel growth is particularly intriguing in thyroid cancer, given the density of blood vessels in thyroid malignancies, says Ezra Cohen, MD, assistant professor of medicine at the University of Chicago. Last October, the *Journal of Clinical Oncology* published results from two phase II studies showing some patients responded to Nexavar (sorafenib)—an agent approved for liver and kidney cancer—and axitinib, which are believed to work at least in part by inhibiting blood vessel growth, specifically receptors for a protein called vascular endothelial growth factor, or VEGF.

In the Nexavar study, seven of the 30 patients with advanced disease had a partial response (tumor shrinkage of at least half) to the drug that lasted 18 to 84 weeks. The cancer stabilized in another 16 patients for 14 to at least 89 weeks.

The axitinib study, which involved 60 patients with advanced cancer, found that 18 patients experienced a partial response to the drug. In another 23 patients the cancer stabilized for at least 24 weeks.

“I think we can safely say from this study that this drug (axitinib) has activity,” says Cohen, the study’s lead author. “The question really is, does it ultimately improve [overall] survival in this disease?”

Other drugs for advanced or radioactive iodine-resistant malignancies also have garnered encouraging, albeit early, results. In July of 2008, a phase II study published in *The New England Journal of Medicine* reported that motesanib (AMG 706) achieved a partial response in 13 of 93 patients who took the drug. In 62 patients, the cancer stabilized, lasting at least 24 weeks in 33 of the 62 patients.

Steven I. Sherman, MD, chair of the department of endocrine neoplasia and hormonal disorders at M.D. Anderson Cancer Center in Houston and lead author of the *NEJM* study, is researching another drug that he describes as promising in medullary cancer. Called XL184, the drug targets VEGF and other receptors, including RET. (A mutation of the RET gene, which can run in families, is strongly associated with medullary cancer and other endocrine malignancies.)

The phase I trial of 84 patients, including 36 with medullary thyroid cancer, found XL184 to be generally well tolerated. In a subset of 22 medullary patients who took the drug for at least three months, 12 patients experienced a partial response, according to results presented at the Molecular Targets and Cancer Therapeutics conference last October. By year’s end, medullary cancer patients were being enrolled in a phase III trial with XL184.

Another investigational drug for medullary cancer, Zactima (vandetanib), may be closer to approval, Sherman says. A randomized phase III trial studying Zactima wrapped up in 2008.

As these and other promising drugs are identified, physicians will be able to transform difficult-to-treat thyroid malignancies into chronic conditions, rather than lethal ones, Sherman says. “This is clearly where we are headed,” he says. “This isn’t a conversation we could have had three years ago.”

In 2001, once the medullary cancer had spread to his organs, Troupp was given no treatment options until his physician learned of a clinical trial. That first drug, oral suberoylanilide hydroxamic acid (SAHA), now marketed under the brand name Zolinza (vorinostat) for a type of lymphoma, halted the cancer’s spread for more than five years, Troupp says. Last summer, Troupp switched to a phase I study of XL184 after scans showed cancer advancing in his liver and his bones. By year’s end, two sets of scans showed the cancer had stalled again.

Troupp has been retired since 2005, after cancer-related fatigue made it impossible to keep pace with his 750-family congregation in Commack, New York. But he credits these two experimental drugs with buying crucial years, time with his wife, and an occasional evening at the theater when his energy allows.

In the meantime, Troupp closely monitors the latest clinical trials. “I fully expect that I’ll ride this horse (XL184) for as long as I can, and then I’ll look for a new mount.”