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FEATURE STORY

Bladder Cancer: Breaking the Research Barrier

BY BEVERLY A. CALEY

“I am convinced I will die in front of a truck or by falling off a mountain or of a heart attack. I do not believe this is going to kill me.” Thomas Touzel’s confidence comes despite having already been through four surgeries to remove dozens of tumors from his bladder.

Diagnosed in 2003 at the age of 64, right now he feels great. Most cases of bladder cancer are chronic but treatable, while others are lethal within a year or two. Touzel has the more treatable type. “They do a scope and do some chop-chop when necessary,” is how he describes his ongoing treatment. “It’s just a question of maintenance.”

Of the more than 61,000 new cases of bladder cancer estimated for the United States in 2006, about 90 percent will be in people over age 55 and nearly 45,000 will be men—white men for the most part. Although progress is being made in understanding the origins and development of the disease, experts say insufficient funding, poor accrual to clinical trials and lack of public awareness of bladder cancer have left promising new treatments under-researched.

Thomas Touzel was diagnosed more than three years ago with a less aggressive form of bladder cancer. Photo by David Gresham

Obstacles to New Treatments

Despite its ranking as the sixth most common cancer in the United States, according to the American Cancer Society, and a recurrence rate of at least 50 percent, the biggest challenge in terms of developing new treatments is enrolling patients in clinical trials, says Walter Stadler, MD, director of the genitourinary program at the University of Chicago Hospitals. Smoking is the biggest risk factor for bladder cancer, so since the disease mainly afflicts men who smoke and have concurrent diseases, “smoking history and things like hypertension and prior surgeries mean that these patients often have problems with kidney function, and that limits our ability to give certain chemotherapy drugs,” Dr. Stadler explains. Delayed enrollment also impacts eligibility. “By the time oncologists run out of options, the patients are too sick to enter a clinical trial,” says Dr. Stadler.

Funding for bladder cancer research is also an issue. Michael O’Donnell, MD, director of urologic oncology at the University of Iowa Hospitals, says researchers have made some promising discoveries in laboratory experiments for a possible vaccine that could target specific attributes of bladder cancer tumors. “Unfortunately, there is not much commercial interest in this kind of development,” Dr. O’Donnell says. While a lack of interest may in part stem from the perception of bladder cancer as an “old white man’s disease,” those affected are starting to take action.

A 2002 national task force identified the need for a nationwide advocacy group for bladder cancer to help establish research priorities at the national level and advocate for scientific studies and clinical trials. Three years later, the wife of a bladder cancer patient founded the Bladder Cancer Advocacy Network.

Diane Zipursky Quale, whose husband John was diagnosed with bladder cancer in 2000, says cancers for which a lot of new research is being done can be traced in part to the patient advocacy groups. “So much is being done in breast cancer, prostate cancer and colon cancer, in large part because the advocacy groups stepped forward and said, ‘We need something better.’ ” Zipursky Quale hopes BCAN will increase awareness and engage the bladder cancer community so that more research funds will be devoted to exploring better treatments.

“Groups like BCAN can make a big impact,” says Dr. Stadler. “Getting patients, community physicians and everybody on the same page is a very important step.” He also urges patients to get more involved in their care. “It would go a long way in galvanizing some of the research efforts out there if the patients would ask, ‘Why are we doing this? How could we make this better?’ ”

Touzel did just that. After researching emerging treatments for bladder cancer, he moved more than 1,100 miles from Florida to Texas to be near M.D. Anderson Cancer Center in Houston. “I’m not a rocket scientist, but within days I knew where I wanted to be and what doctor I wanted to treat me,” Touzel says.

Mistaken Identity

Pat Screeden of St. Charles, Illinois, was 54 when she first noticed a small amount of blood in her urine, known as hematuria, in December 2003. She received a prescription for antibiotics for what was thought to be an infection. About six weeks later, the hematuria showed up again and she was given another round of antibiotics. When the hematuria returned yet again a month later, Screeden consulted a urologist. Several tumors were revealed during a procedure known as a cystoscopy in which a thin tube with a lens and light (a cystoscope) is placed in the bladder through the urethra.

People should not ignore blood in their urine, says Dr. O'Donnell. "It's not normal and it isn't always a simple urinary tract infection. If they have no symptoms of infection, they should consider that bladder cancer is a possibility and ask their physicians."

When bladder cancer is suspected, cystoscopy is the most common diagnostic test. In addition to enabling the physician to see inside the bladder to determine if tumors are present, cystoscopy allows tissue samples to be taken for a biopsy. Another common test is urine cytology, which examines urine under a microscope for abnormal cells.

A new diagnostic tool for the detection of bladder cancer is known as fluorescence cystoscopy, which uses a photosensitizing agent known as hexaminolevulinate (HAL) that is administered within the bladder. Studies have shown that HAL fluorescence cystoscopy is able to identify very early-stage bladder tumors that are not visible with conventional white-light cystoscopy.

A more modern type of test uses chemicals or antibodies to identify specific substances released by cancer cells that may be present in urine. About 20 such tests are available for bladder cancer diagnosis, but the Food and Drug Administration has approved only a handful, including ImmunoCyt™, NMP22 BladderChek® and UroVysion™, each of which looks for a different substance. These tests are not accurate enough to replace cystoscopy, but a major effort is under way to develop a urine-based test that could, says Dr. O'Donnell.

The biopsy taken during cystoscopy reveals the specifics of the bladder cancer, including type, stage and importantly, the grade. Grade indicates the aggressiveness of the cancer with designations of low-grade or high-grade cancer, each of which behaves very differently in terms of tumor biology and prognosis.

Low-grade noninvasive bladder cancer accounts for about 80 percent of cases and is often multifocal, meaning several tumors form simultaneously at different locations within the bladder. Two theories attempt to explain the multifocal nature of these tumors. The first identifies bladder cancer as a so-called field disease, a concept first introduced in 1953 that suggests tumors develop independently because the entire field of tissue presumably has more prolonged exposure to environmental carcinogens in the urine. The second, known as the monoclonality theory, is supported by genetic studies that point to seeding of cancer cells in the urinary tract that originated from a single primary tumor.

Patients with low-grade disease often have recurrences, with only about 15 percent progressing to invasive cancer. High-grade, muscle-invasive bladder tumors are much more severe for the 20 percent of patients diagnosed. More

than 50 percent of these patients experience metastasis despite aggressive treatment.

View Illustration: Invading the Bladder

Diverting the Flow

Once doctors make a detailed diagnosis, surgery, chemotherapy, immunotherapy and radiation can be used in various combinations, depending on the stage and aggressiveness of the cancer. For early-stage bladder cancer, surgeons often remove tumors with a decades-old procedure called transurethral resection of the bladder, or TURB. The surgeon inserts a type of cystoscope called a resectoscope into the bladder through the urethra. The device contains a small wire loop at the end that is used to remove the tumors. Fulguration often accompanies TURB, in which cancer cells are burned away with an electrical current. In addition to its therapeutic use, TURB also provides doctors with tissue for determining the type, grade and stage of the tumor.

If bladder cancer has invaded the muscle beyond the inner bladder lining, a radical cystectomy is done to remove the bladder and nearby organs and lymph nodes. Researchers are looking into whether partial cystectomy, during which surgeons remove only part of the bladder, may be an option for some patients in order to retain bladder function. Experts, however, disagree about the usefulness of this treatment since most bladder cancers involve several sites in the bladder and the risk of recurrence is higher when only part of the bladder is removed.

Patients who have their bladders removed must undergo reconstructive surgery to create a new method for the body to store and drain urine. Screeden had tumors removed in a TURB procedure, but after tests found her cancer was in multiple locations, her bladder was removed. Doctors constructed a new bladder for her through a urinary conduit, a simple operation where a segment of the small intestine directs urine through a stoma into an external collecting bag.

An option that eliminates the need for an external bag is a catheterizable stoma, an internal pouch that is drained using a catheter. The most complex reconstruction procedure involves the surgeon essentially creating a new bladder, or neobladder, where the intestine is made into a storage area and attached to the urethra.

Adding Drug Therapy

TURB is usually followed by treatment administered within the bladder to rid the organ of any tumor cells that broke off during TURB. Called intravesical therapy, this type of immunotherapy uses the body’s own immune system to fight cancer. The agent most often used for intravesical treatment is bacillus Calmette-Guérin (BCG), a form of bacteria that is sometimes used as a tuberculosis vaccine. The treatment is typically given once a week for six weeks, and although much of the drug is washed out during urination, a good amount remains in the bladder.

Researchers believe BCG works by alerting the cells lining the bladder of a

brewing infection, which results in infection-fighting white blood cells rushing to the bladder. But unlike the normal chain of events that occurs with urinary tract infections, Dr. O'Donnell says BCG causes the white blood cells to release a tumor-killing compound called TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) that is effective in destroying cancer cells but spares normal cells. Chemotherapy agents, such as Valstar® (valrubicin), Mutamycin® (mitomycin), Adriamycin® (doxorubicin) or Thioplex® (thiotepa), may also be used for intravesical therapy.

A standard of care for cancer that has spread outside the bladder involves a combination of Gemzar® (gemcitabine) and cisplatin, therapy that John Quale received after multiple tumors were found in his bladder that had spread to his liver and nearby lymph nodes.

Before his wife created BCAN in 2005, Quale, now 60, experienced numerous recurrences that led to additional surgeries and chemotherapy treatments. He's currently recovering from having his bladder removed this past September.

Another cisplatin-based chemotherapy known as M-VAC, a combination of methotrexate, Velban® (vinblastine), Adriamycin and cisplatin, has "essentially fallen out of favor" because of its side effects, says Maha Hussain, MD, professor of internal medicine at the University of Michigan. She says the combination of cisplatin and Gemzar is now most commonly used in clinical practice.

Currently, data fail to show a benefit for treatment given after surgery, but for patients who receive chemotherapy before surgery, studies have shown statistically significant improvements in both overall survival and disease-free survival. Dr. Hussain says newly diagnosed early-stage bladder cancer patients should discuss this option with their oncologists before surgery. "It doesn't mean they have to take the chemotherapy. It means they know their options," she says.

Cancer Targets

Most bladder cancer clinical trials are exploring different combination regimens of chemotherapy, targeted agents and immunotherapy. Recently, investigators combined Herceptin® (trastuzumab) with standard chemotherapy after tests found that about half of patients had excess HER2 on the surface of their bladder cancer cells. Herceptin blocks the effects of the growth factor protein HER2, which transmits growth signals to cancer cells. Early results show that 70 percent of patients are responding to the drug. Further testing is expected that will compare chemotherapy with and without Herceptin.

Another new combination is BCG with interferon, which stimulates the growth and action of immune system cells that fight disease and infection. The combination was effective in patients regardless of whether they received previous treatment with BCG. Dr. O'Donnell, the trial's lead investigator, says the combination worked particularly well for patients with high-grade disease, though older patients did not respond well to the combination.

Javlor® (vinflunine), the newest drug in a class of agents known as vinca alkaloids, is in phase III testing for bladder cancer. Researchers are also testing kidney cancer drugs Sutent® (sunitinib) and Nexavar® (sorafenib) and colorectal and lung

cancer drug Avastin® (bevacizumab) in hopes of duplicating the drugs' response rates for bladder cancer by targeting the pathway that promotes blood vessel formation and proliferation of tumor cells. Other novel bladder cancer treatments in development include E7389, a synthetic version of halichondrin B, which is a naturally occurring substance found in South Pacific sea sponges, and Alimta® (pemetrexed), a therapy approved for lung cancer.

Doctors and patients agree that current treatments for bladder cancer are not good enough, and despite studies testing targeted agents and other combination regimens, more must be done. For patients with locally advanced disease, better chemotherapies before surgery could lengthen survival, and better treatments after surgery could reduce high recurrence rates. Experts say effort also needs to be focused on improving therapy for patients with metastatic disease. Bladder cancer patients and their families can help change the status quo by demanding new treatments. Dr. Hussain says improvements in survival can only come from better treatments. "Doctors and patients must partner in discovering them."