Preventing Postoperative Urinary Tract Infections in Cancer Patients

By Laura L. Russell

Urinary tract infections (UTIs) increase morbidity, mortality, and health care costs and prolong hospitalizations for patients who require urinary catheters—especially those who undergo long, complex surgeries or procedures to treat urological or gynecological cancers. To reduce the incidence of UTIs, clinicians at The University of Texas MD Anderson Cancer Center developed a quality improvement program for surgical patients at the institution.

Nationwide, postoperative UTIs occur in 2%–5% of surgical patients. In 2011, surgeons at MD Anderson reviewed the records of approximately 800 consecutive surgical patients and found that UTIs occurred within 30 days after surgery in 2.9% of the patients. The surgeons compared this rate with the rates at other member institutions of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP), which maintains a database of patient outcomes. The analysis indicated that although MD Anderson’s postoperative UTI rate was lower than the rates seen at many institutions, there was room for improvement. For that reason, UTIs became the focus of a data-driven quality improvement effort within the Division of Surgery.

The rate of urinary tract infections in patients who underwent surgery at MD Anderson has decreased since the second quarter of 2012, when the S.T.O.P. UTI program was launched with the goal of preventing such infections.
“MD Anderson is a remarkable place in terms of being data driven,” said Thomas Aloia, M.D., an associate professor in the Department of Surgical Oncology and the institution’s liaison with the ACS. “When we have presented people at the institution with data that say we can do better, we’ve yet to encounter resistance to improvement from anyone. Our providers want to improve, and they want the best outcomes for our patients.”

**Reducing UTI rates**

To address the issue of UTIs, the Division of Surgery assembled a team of surgeons, nurses, anesthesiologists, pharmacists, advanced practice providers, trainees, and environmental engineers to examine the institution’s use of urinary catheters, which are used in almost all patients who undergo surgery in the institution’s main hospital. The team instituted a quality assessment and improvement program called S.T.O.P. UTI, which was named for the program’s four aspects of catheter management:

- sterile placement of the catheter,
- timely removal of the catheter,
- optimal positioning of the catheter (i.e., to avoid reflux of urine into the bladder), and
- proper sampling (i.e., obtaining clean urine samples to validate a diagnosis of UTI).

The initial assessment helped the team target areas for improvement, which included changes to nursing protocols and consolidation of materials required for catheter placement. From 2012, when S.T.O.P. UTI was launched, to 2015, postoperative UTI rates at MD Anderson dropped from 2.90% to 0.46%. And there was an added bonus: the UTI rates for patients who had urinary catheters placed but did not undergo surgery also fell, from 2.4% in 2014 to 0.6% in 2015, even though S.T.O.P. UTI was an improvement program specific to the Division of Surgery.

“There were no simultaneous programs in other divisions to explain those results,” Dr. Aloia said. “So we concluded that the lessons learned in the early part of the surgical quality improvement program had diffused to the whole institution. The ACS searched the literature, and as far as they can tell, this is the first instance of a surgical quality improvement program of this type spreading institution-wide. Significant credit needs to be given to the nursing staff, who were involved in the process improvement from the beginning and applied the new nursing protocols to all hospitalized patients with urinary catheters, not just surgical patients. Ultimately, the whole hospital benefitted.”

The initial report on the S.T.O.P. UTI initiative was presented at the 2014 ACS NSQIP Annual Conference; and at the 2016 conference this July, Dr. Aloia and his colleagues gave a follow-up presentation about the program’s institution-wide impact. Since then, institutions around the country have contacted MD Anderson to ask about the program.

“The S.T.O.P. UTI program is a tool that any institution can use to evaluate its procedures for catheter use, find any weak links, and fix them.”

– Dr. Thomas Aloia

A recent study’s findings provide a starting point for assessing the efficacy of immunotherapy in rectal cancer patients with deficient DNA mismatch repair (dMMR).

dMMR status has long been established as an important prognostic biomarker in colorectal cancer, but breakthroughs in therapy for dMMR-associated disease have been slow in coming, said Y. Nancy You, M.D., an associate professor in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center and the study report’s senior author. However, recent developments in cancer immunotherapy are changing this paradigm. Early trials in patients with colorectal and other cancers have demonstrated that patients with dMMR have better responses to immunotherapy drugs, particularly immune checkpoint inhibitors, than do those without dMMR. Now, additional clinical trials of immunotherapy with or without conventional therapy for patients with dMMR-associated colorectal cancer are rapidly gathering on the horizon.

“All of a sudden, several forces are coming together: we have this cohort of patients with a genetically defined syndrome, and there’s this phenomenal approach to treatment that’s becoming available to them,” Dr. You said. “But at the same time, it’s never been established how the subset of patients with dMMR rectal cancer specifically do with just conventional therapy.”

Thus, Dr. You and her colleagues designed a retrospective study to assess the outcomes of patients with dMMR rectal cancer following standard multimodality therapy. This information can provide a baseline for comparison when such patients are enrolled in the upcoming clinical trials of new immunotherapies. Although the implications of dMMR status in colon cancer patients have been largely defined—in general, patients with dMMR have a better prognosis than those without dMMR—these implications were not known in rectal cancer patients. The recent study showed that the prognosis of rectal cancer patients with dMMR tended to be much better than that of rectal cancer patients without dMMR.

The study also demonstrated that currently available multimodality therapy for dMMR rectal cancer offers a chance at a cure. Patients with stage I or II disease had a 5-year rectal cancer–specific survival rate of 100%, and those with stage III and IV disease had 5-year rectal cancer–specific survival rates of 85% and 60%, respectively. The vast majority of patients (95%) underwent surgical resection with curative intent, and most of those patients
Deficient DNA Mismatch Repair in Rectal Cancer Patients

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“Since we can precisely define the key genetic defects that drive this cancer, we can more accurately predict its prognosis.”

– Dr. Y. Nancy You

(66%) received adjuvant chemotherapy. About three-fourths of the patients with stage III or IV disease also received neoadjuvant fluoropyrimidine-based chemotherapy and pelvic radiation therapy; this regimen was associated with a complete pathological response rate of 28%.

The study’s findings also confirmed the importance of screening rectal cancer patients for dMMR. dMMR is the hallmark of Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer), a hereditary cancer disorder that increases patients’ lifetime risk for colorectal and other cancers and has implications for patients’ blood relatives. Lynch syndrome is caused by defects in mismatch repair genes including MLH1, MSH2, MSH6, and PMS2.

Most patients in the study had Lynch syndrome, and most of these patients had pathogenic germline mutations in the MSH2 or MSH6 genes. Defects in the MSH2 and MSH6 genes can predispose patients to colorectal cancer, but they are also associated with other cancers. About one-fifth of the dMMR rectal cancer patients in the study had a history of at least one non-colorectal cancer before their diagnosis, and another fifth developed at least one non-colorectal cancer during the follow-up period.

“Since we can precisely define the key genetic defects that drive this cancer, we can more accurately predict its prognosis, the drugs or other therapies it will respond to, and the implications in terms of patients’ long-term survivorship,” she said. “We’re testing other cancers for various mutations to find new pathways to target therapeutically, but dMMR screening in patients with rectal cancer is an example that’s here today.”

FOR MORE INFORMATION
Dr. Y. Nancy You ....................713-794-4206

FURTHER READING

CLINICAL TRIALS: Colorectal Cancer Treatment

Pilot study assessing the safety and tolerability of the neoadjuvant use of tremelimumum (anti–CTLA-4) plus MEDI4736 (anti–PD-L1) in the treatment of resectable colorectal cancer liver metastases (2015-0828). Principal investigator (PI): Dr. Michael Overman. The goal of this study is to learn if the immune checkpoint inhibitor tremelimumum plus MEDI4736 (another immune checkpoint inhibitor), FOLFOX (fluorouracil, leucovorin, and oxaliplatin), and bevacizumab can help to control colorectal cancer that has spread to the liver. The safety of these drugs will also be studied.

Pilot study of the feasibility and safety of a personalized peptide vaccine in patients with advanced pancreatic ductal adenocarcinoma or colorectal adenocarcinoma (2014-1029). PI: Dr. Overman. The goal of this study is to study the safety of a vaccine to treat advanced pancreatic or colorectal cancer. This study will use cells from each patient’s tumor and blood to create a personalized vaccine.

A phase I study of MEDI4736 (anti–PD-L1 antibody) in combination with tremelimumum (anti–CTLA-4 antibody) in subjects with advanced solid tumors (2014-1052). PI: Dr. Aung Naing. The goal of this study is to find the highest tolerable dose and optimal dosing schedule for a combination of MEDI4736 (durvalumab) and tremelimumum in patients with advanced cancers, including colorectal cancer.

A first-in-human study of repeat dosing with REGN2810, a monoclonal, fully human antibody to programmed death-1 (PD-1), as single therapy and in combination with other anti-cancer therapies in patients with advanced malignancies (2015-0261). PI: Dr. Naing. The goal of this study is to find the highest tolerable dose of REGN2810 given alone; with radiation; with cyclophosphamide; with both radiation and cyclophosphamide; with radiation, cyclophosphamide, and granulocyte-macrophage colony-stimulating factor; with docetaxel; or with docetaxel and carboplatin.

FOR MORE INFORMATION
Visit www.clinicaltrials.org
By Joe Munch

More than one-third of adolescents and young adults diagnosed with colorectal cancer have hereditary disease, according to a study from The University of Texas MD Anderson Cancer Center.

The study's findings, which come amid an uptick in the prevalence of colorectal cancer among people younger than 50 years, underscore the need for such patients to be evaluated by a genetic counselor.

The retrospective study, the largest of its kind to date, reviewed data from about 200 colorectal cancer patients age 35 years or younger who received genetic counseling and testing at MD Anderson between 2009 and 2013.

“What we discovered was that more than a third—35%—of the patients had a hereditary colorectal cancer syndrome, which is kind of astounding because previous literature has reported that the frequency of hereditary colorectal cancer in the general colorectal cancer population is only 5%,” said Eduardo Vilar-Sanchez, M.D., Ph.D., an assistant professor in the Department of Clinical Cancer Prevention and the study’s senior author.

Most patients with hereditary colorectal cancer in the study had Lynch syndrome (45 patients) or familial adenomatous polyposis (16 patients). Lynch syndrome conveys a lifetime colorectal cancer risk of up to 80%, and familial adenomatous polyposis in the absence of screening, surveillance, and prophylaxis all but guarantees that colorectal cancer will develop.

“A diagnosis of hereditary cancer has implications for a wider population because that diagnosis extends to the rest of the family,” Dr. Vilar-Sanchez said. “Those family members will need to undergo genetic testing, and if they are diagnosed with a genetic condition, they will need to be doing surveillance and screening.”

Of note, Dr. Vilar-Sanchez said, a substantial proportion of patients with hereditary colorectal cancer in the study were the first in their families to be diagnosed with a hereditary syndrome. In addition, 13 of the patients with hereditary colorectal cancer had germline mutations and no family history of disease. The findings suggest that all patients age 35 years or younger who are diagnosed with colorectal cancer should be referred to receive genetic counseling about hereditary cancer syndromes regardless of their family history.

The study also found that patients with hereditary colorectal cancer were less likely than patients with nonhereditary colorectal cancer to have features indicative of aggressive disease, including left-sided tumors, metastatic disease, poorly differentiated tumors, and tumors with signet ring cells. No such differences were observed among patients with different hereditary syndromes, Dr. Vilar-Sanchez said, noting that the pathological characteristics of tumors from patients with Lynch syndrome were not substantially different than those from patients with familial adenomatous polyposis.

The main takeaway from the study’s findings, Dr. Vilar-Sanchez said, is that there should be a strong suspicion for a hereditary syndrome in patients age 35 years or younger who present with colorectal cancer.

“At some point, most physicians who treat colorectal cancer will probably be caring for a patient who has a hereditary condition, and that requires some extra considerations for their care and has implications for their family members,” Dr. Vilar-Sanchez said.

FOR MORE INFORMATION
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FURTHER READING

Infusion of Natural Killer Cells into the Brain Shows Promise against Medulloblastoma, Other Posterior Fossa Tumors

By Bryan Tutt

Medulloblastomas, the most common malignant brain tumors in children, are usually incurable if they recur. But a clinical trial of a novel therapy in which natural killer (NK) cells are infused directly into the brain is now enrolling young patients with recurrent medulloblastoma and other malignant tumors of the posterior fossa.

Medulloblastomas recur in 20%–30% of pediatric patients after standard treatment with surgery followed by concurrent chemotherapy and radiation therapy and then adjuvant chemotherapy or—for children younger than 3 years—surgery followed by high-dose chemotherapy and stem cell transplant. Less common malignant tumors of the posterior fossa, which include ependymomas and atypical teratoid rhabdoid tumors, also have high recurrence rates and carry poor prognoses.

The current treatment for recurrent medulloblastoma is salvage chemotherapy and, for patients at least 3 years old, re-irradiation. Even with treatment, patients with recurrent medulloblastoma have a 2-year overall survival rate of less than 20%.

“We need to find novel therapies for posterior fossa tumors that can have a meaningful effect on survival,” said Soumen Khatua, M.D., an associate professor and chief of the Pediatric Neuro-oncology Section in the Division of Pediatrics at The University of Texas MD Anderson Cancer Center.

NK cells for cancer treatment

Dr. Khatua is the principal investigator of a clinical trial (No. 2013-0765) in which autologous NK cells are injected directly into patients’ brains. The trial is currently enrolling patients younger than 22 years with recurrent malignant tumors of the posterior fossa. Dr. Khatua said that most patients in the study so far have undergone at least one failed attempt at salvage therapy.

For each patient in the study, NK cells are harvested from the patient’s blood, expanded, and cryopreserved until the time of infusion. A catheter is placed in the patient’s fourth ventricle, and the autologous NK cells are infused through the catheter. The patient receives three cycles of treatment with NK cells; each cycle comprises three infusions per week for 3 weeks followed by 1 week of rest. Three months after the completion of treatment, the patient will undergo magnetic resonance imaging to assess the tumor response.

“We have performed more than 50 infusions and seen no dose-limiting toxicities,” Dr. Khatua said. “This is a dose-escalating trial, and we have gone to the second of three dose levels.”

Preliminary results of the trial are not yet available, but preclinical studies showed that NK cells had antitumor activity against medulloblastoma and atypical teratoid rhabdoid tumor cell lines. Mouse xenograft models of medulloblastoma confirmed this activity. These studies and the resulting clinical trial were developed by a team that included (in addition to Dr. Khatua) Laurence Cooper, M.D., Ph.D., Vidya Gopalakrishnan, Ph.D., Wafik Zaky, M.D., and Dean Lee, M.D., Ph.D., respectively a visiting scientist, associate professor, assistant professor, and former associate professor in the Division of Pediatrics; and David Sandberg, M.D., and Jeffrey Weinberg, M.D., both professors in the Department of Neurosurgery.

Future directions

Because the ongoing clinical trial is the first to infuse NK cells directly into the brain, several precautions were taken for safety. One of these was infusing three doses of NK cells per week instead of one large, weekly dose. Because of the proven safety of the initial infusions, the researchers have proposed an amendment to the trial’s protocol so that the entire dose for each week can be given in one infusion instead of three.

Another safety provision was the use of autologous rather than allogeneic NK cells. However, because the preclinical studies that led to the trial used allogeneic NK cells, Dr. Khatua and his colleagues think allogeneic NK cells or “off-the-shelf” NK cell products might be more efficacious than autologous NK cells in clinical use. “Now that the safety of autologous cells appears to be established, and hopefully will be further established, the next step will likely be to use allogeneic or off-the-shelf NK cells,” Dr. Khatua said.

Finally, Dr. Khatua and his colleagues would like future trials to investigate whether NK cell infusion will have synergy with chemotherapy drugs against malignant posterior fossa tumors. Dr. Khatua said, “It is imperative that we find novel therapies including biologic agents that can be directly infused into the brain to fight these tumors in close proximity and yet prevent toxicity from systemic chemotherapy.”

FOR MORE INFORMATION
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Vitamin D and Cancer Prevention

Research is promising but still inconclusive

Known as the “sunshine vitamin,” vitamin D has been shown to improve bone, thyroid, and kidney health by regulating calcium and phosphate levels in the body. Recent studies also suggest adequate or above-average levels of vitamin D may help prevent or slow the development of some cancers, but more evidence is needed to confirm these findings.

“We have a lot of interest in vitamins and supplements and how they relate to cancer,” said Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention and the medical director of the Cancer Prevention Center at The University of Texas MD Anderson Cancer Center. “Currently, there are very limited data—especially high-level data—that can guide clinical recommendations. But there is some evidence that suggests certain vitamins or supplements may be beneficial in reducing the risk of developing cancer, and one of these is vitamin D.”

How the body processes vitamin D

When exposed to ultraviolet light from the sun, the human body produces vitamin D. The liver then converts vitamin D into 25-hydroxyvitamin D, also called 25(OH)D, which travels through the bloodstream to the kidneys, where it becomes the active form of vitamin D that can be used by the body.

Although sunlight exposure increases the risk of skin cancer, the vitamin D that results from such exposure may reduce the risk of other cancers. Research in the 1980s showed that the rate of developing or dying of certain cancers was lower among people living in southern parts of the United States than in those living in the north, where there is less sunlight.

In addition to sunlight exposure, people can get vitamin D by eating fatty fish, such as salmon and tuna, as well as fortified milk and cereals. For people who live in less sunny climates or do not eat fish, vitamin D supplements are the most convenient option.

Research findings

Studies have indicated that vitamin D supplements may decrease a person’s risk of breast, colorectal, pancreatic, and prostate cancers. However, these studies were not conclusive. And in a study done this year at the University of California, San Diego, School of Medicine, the participants (all women) who had high levels of vitamin D in their blood had a 67% lower cancer risk compared with women whose vitamin D levels were lower, suggesting that higher vitamin D levels decrease the risk of developing cancer.

In another recent study, researchers at Stanford University School of Medicine found that breast tumors grew faster and spread to more parts of the body in mice with low vitamin D levels than in mice with adequate levels. Dr. Bevers said that this finding suggests that vitamin D may have properties that can slow or prevent the development of cancer, but she added that what happens in a mouse does not necessarily happen in a human.

According to Dr. Bevers, a link between cancer and vitamin D has not been proven in clinical trials. In fact, it is difficult for clinical trials to determine the effect of vitamin D supplements on cancer risk because a person’s diet and the amount of time spent in the sun also affect that person’s vitamin D level.

Getting enough vitamin D

Most experts recommend a daily vitamin D intake of 400 international units (IU) for children younger than 1 year, 600 IU for people 1–70 years old, and 800 IU for those older than 70 years. However, these daily allowances were based on the vitamin’s effect on bone health rather than its potential for cancer prevention.

“At this time, we do not make any recommendations regarding vitamin supplements for cancer prevention,” Dr. Bevers said. “That’s not to say there isn’t ongoing research, but we need to have more conclusive evidence before making those recommendations.”

– Z. Ahmed

FOR MORE INFORMATION
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• Call askMDAnderson at 877-632-6789
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The clinic, which is under the umbrella of MD Anderson’s Clinical Cancer Genetics Program, offers genetic counseling, diagnostic testing, cancer surveillance, and prophylactic surgery for these patients and their family members.

Y. Nancy You, M.D., an associate professor in the Department of Surgical Oncology and the leader of the clinic, estimates that she and her colleagues follow about 400 families with hereditary gastrointestinal cancer syndromes, including Lynch syndrome.

“Most oncologists might see only a handful of patients with Lynch or other inherited cancer syndromes, and without an established infrastructure, it can be difficult to identify these patients and provide comprehensive care for them across the cancer spectrum, from diagnosis to treatment to prevention and screening to research,” Dr. You said. “With this clinic, we have the infrastructure and expertise necessary to serve these patients and their families in a comprehensive fashion.”

In addition to Dr. You, the core faculty members of the clinic include Eduardo Vilar-Sanchez, M.D., Ph.D., an assistant professor in the Department of Clinical Cancer Prevention, Patrick Lynch, M.D., a professor in the Department of Gastroenterology, Hepatology, and Nutrition, and Miguel Rodriguez-Bigas, M.D., a professor in the Department of Surgical Oncology.

“We are unique in this regard because we have a group of dedicated individuals who have focused their efforts on helping patients with these genetic diseases, which are relatively rare,” Dr. Vilar-Sanchez said.

The clinic also provides the means to conduct research into the causes, management, and prevention of hereditary gastrointestinal cancers. Current efforts enabled by the clinic include a trial of naproxen for the prevention of colorectal cancer in people with deficient DNA mismatch repair and the establishment of an online registry for communicating the results of genetic testing to as many at-risk family members as possible.