Preoperative Chemotherapy Offers Best Outcomes for Patients with Rare Bladder Cancer

By Amelia Scholtz

A combination of neoadjuvant chemotherapy and surgery provides patients who have small-cell urothelial cancer (SCUC) with much longer survival times than does initial surgery, the previous standard treatment.

These improved survival times were shown in a retrospective study in which a team of investigators reviewed the records of 172 patients treated for SCUC at The University of Texas MD Anderson Cancer Center between 1985 and 2010. The findings were striking. The median overall survival time for patients treated with initial surgery—which is still considered the standard treatment at many institutions—was only 18.3 months. In contrast, the median overall survival time for patients treated with neoadjuvant chemotherapy followed by surgery was 159.5 months—more than 13 years. Five-year disease-specific survival rates also differed markedly: 20% for those treated with initial surgery and 79% for those who received neoadjuvant chemotherapy and surgery.

Overall (left) and disease-specific survival from the time of diagnosis with small-cell urothelial cancer in patients undergoing neoadjuvant chemotherapy and cystectomy compared with those undergoing initial cystectomy. Adapted from Lynch SP, et al. Eur Urol 2012.
SCUC represents less than 1% of bladder cancers. The patients are usually men between 60 and 80 years old who have a history of smoking or contact with industrial carcinogens. Relative to other bladder cancers, SCUC has a high potential for rapid growth and for the development of microscopic metastases. These characteristics have made SCUC notoriously difficult to treat.

The infrequency with which SCUC is seen by oncologists has hampered research progress. Studies of SCUC have small patient sample sizes, and research funding is small relative to funding for more common cancers. Thus, the publication of a long-term retrospective study that finds SCUC tumors to be particularly sensitive to chemotherapy is especially noteworthy. “The study demonstrated that neoadjuvant chemotherapy really provides an opportunity to cure people who otherwise would have died of their cancer,” said corresponding author Arlene Siefker-Radtke, M.D., an associate professor in the Department of Genitourinary Medical Oncology.

**Chemotherapy**

One of the study’s other notable findings was that postoperative chemotherapy offers little additional benefit to SCUC patients undergoing initial surgery. One reason for the discrepancy in the benefits of neoadjuvant (preoperative) and adjuvant (postoperative) chemotherapy is that patients can begin chemotherapy much more quickly than they can be scheduled and prepared for surgery. While waiting for surgery, SCUC patients who are not undergoing chemotherapy may experience rapid tumor growth, resulting in surgeons’ finding much more advanced disease than clinical staging had suggested. These patients also may develop clinically evident metastatic disease during the postoperative recovery period—which can last 2–3 months—before adjuvant chemotherapy begins. With these possibilities in mind, it is perhaps unsurprising that patients who underwent surgery followed by chemotherapy had a median overall survival time of 18.1 months, which was not significantly different from that of patients who underwent surgery alone.

The benefits of neoadjuvant chemotherapy plus surgery relative to both surgery alone and surgery followed by chemotherapy are also apparent when one considers disease staging. Whereas 62% of patients treated with neoadjuvant chemotherapy had their disease downstaged to stage I or below at surgery, only 9% of patients who underwent initial surgery had their disease similarly downstaged. Patients with lower stage tumors at surgery have a higher likelihood of cure than do patients with higher stage tumors. Over the years, MD Anderson physicians have been able to refine SCUC chemotherapy regimens to maximize their efficacy. “Initially, we were using bladder cancer regimens for neoadjuvant chemotherapy, but then we’d take patients to surgery and find we weren’t achieving complete eradication of the small-cell malignancy,” Dr. Siefker-Radtke said. This led to the development of a new standard SCUC regimen that alternates between cycles of drugs that target small-cell tumors, such as etoposide and cisplatin, and those that target bladder cancer, such as ifosfamide and doxorubicin.

In addition to varying the drug types, oncologists must vary the number of chemotherapy cycles according to the individual patient’s needs. For most patients, four cycles of neoadjuvant chemotherapy will offer optimal results. For patients with stage III or IV cancer, doctors aim for around six cycles to maximize the response to therapy.

**Surgery and radiation therapy**

Surgery for SCUC varies less than chemotherapy. For most patients, neoadjuvant chemotherapy is followed by either cystectomy or cystoprostatectomy with a lymph node dissection. Patients whose preoperative imaging studies show lymph node involvement are offered surgery only in the setting of a major response to chemotherapy and typically undergo a more extensive lymph node dissection. Of the 172 patients whose cases were reviewed in the study, 125 had surgically resectable disease (clinical stage no higher than T4aN0M0).

It is important to bear in mind that not all SCUC patients are good candidates for the combination of neoadjuvant chemotherapy and surgery. Patients with poor kidney function, heart disease, or advanced emphysema may not have the strength to undergo this aggressive chemotherapy regimen or the surgery that follows it. On a positive note, neoadjuvant chemotherapy may allow patients whose poor condition is
computed tomography shows a small-cell urothelial tumor (arrow) with lymph node metastases before neoadjuvant chemotherapy. The same patient was in complete remission and had no tumor remaining at the time of cystoprostatectomy.

Related to their cancer to improve in condition sufficiently to tolerate surgery.

Patients who are not good candidates for surgery may be considered for a combination of chemotherapy and radiation. This combination is not considered as the first option for two reasons. First, radiation therapy does not appear to have the long-term effectiveness of surgery. Second, radiation therapy may increase the risk of recurrence in patients with carcinoma in situ, which is particularly common in the bladders of people with small-cell tumors.

Results of a clinical trial of SCUC treatment conducted at MD Anderson prior to the retrospective study suggested that radiation could have a role in treating brain metastases. As SCUC patients survive longer, these metastases have become more common, affecting about 50% of survivors who had stage III or IV disease. Doctors now consider prophylactic cranial irradiation for these patients.

Moving forward

So, what lies ahead for SCUC research? The nuances of tumor classification may provide one direction for new investigations. Puzzlingly, some bladder tumors that are not classifiable as SCUC appear to behave much like small-cell tumors, giving researchers pause to consider the genetic pathways involved in tumor development. Dr. Siefker-Radtke said, “Looking at the molecular characterization of these rare tumors and the different genes that they express might help us to distinguish between different types of more traditional-appearing bladder cancer.”

Communication between researchers and clinicians at different treatment centers is especially important in clinical research involving SCUC and other rare cancers because individual institutions may see only a few cases of a given cancer. Communication between members of multidisciplinary treatment teams is also essential. “Centers should develop a treatment strategy within their group and maintain cohesion so that everyone treats these rare tumors in the same way,” Dr. Siefker-Radtke said. “If we saw that a treatment regimen or concept didn’t work, we would switch to a different strategy. That’s how we developed our current chemotherapy regimen for SCUC.” Thanks to communication across disciplines and across institutions, neoadjuvant chemotherapy is gaining acceptance in SCUC treatment.

“There is growing awareness that neoadjuvant chemotherapy is beneficial for patients with SCUC, and it’s been the subject of some large meetings and panel discussions,” Dr. Siefker-Radtke said. “This strategy is gaining traction and is becoming more accepted as the standard in treating this rare bladder cancer.”

For More Information

Dr. Arlene Siefker-Radtke.....713-792-2830

Further Reading

Addressing Psychological Concerns for Cancer Patients

By Dawn Chalaire

Despite advances in cancer treatment over the past several years, for many people, a diagnosis of cancer can still feel like a death sentence. The added stress leads to psychological problems for many patients.

“Many cancer patients are overwhelmed,” said Anis Rashid, M.D., an associate professor in the Department of Psychiatry at The University of Texas MD Anderson Cancer Center. “I have seen patients so distressed that they feel they are falling apart and have no control. This leads to increased anxiety.”

In a setting where the goal of everyone involved—oncologists, radiologists, nurses, patients, and family—is eradication of the disease, a patient’s psychological issues can be downplayed or overlooked. But according to Dr. Rashid, anxiety and depression are common among cancer patients and should be viewed in the same way as any physical symptom that causes a patient distress.

“Treating these symptoms is important for the overall well-being of the patient,” Dr. Rashid said. “If patients are hurting, we need to control their pain. If they’re not sleeping, we need to make them sleep better, and if they have a lot of anxiety, we need to treat it.”

Anxiety in cancer patients

A cancer diagnosis triggers anxiety in up to 40% of patients, Dr. Rashid said. The symptoms of anxiety may include feelings of uneasiness, irritability, difficulty sleeping or staying asleep, increased pain perception, and poor memory and concentration. In cancer patients, anxiety is usually worst during the first 3 months after diagnosis. Initially, patients do not know the stage of their cancer or the type of treatment they will receive, and this uncertainty can contribute to their anxiety.

Cancer patients can also be overwhelmed by the volume of information they receive about their disease and its treatment; this information can come from many different sources and is sometimes contradictory. Such information overload, and specifically contradictory information, can cause anxiety. This anxiety makes it even more difficult for patients to process all the information and make treatment decisions.

A diagnosis of cancer can also trigger a period of great upheaval in a patient’s personal life. Some patients’ spouses or partners are not able to handle the stress, and they avoid hospital visits or leave altogether. Even if the partner stays, patients often feel like a burden to their partner, family, and friends. These and other psychodynamic issues must be addressed to control anxiety.

Anxiety and other symptoms that cause patients distress are treated primarily with medications. Dr. Rashid prescribes antianxiety medications such as lorazepam or clonazepam for short-term control of anxiety. If anxiety persists, she prescribes citalopram, escitalopram, or sertraline. For sleep, zolpidem or trazodone is usually prescribed. These drugs play a very important role in controlling anxiety and making patients more comfortable. Before these medications are prescribed, their possible side effects are discussed with the patients.

“My strategy is that the patient should not suffer emotionally because of pain, poor sleep, or increased anxiety. There are medications to help and to control these symptoms,” Dr. Rashid said.

Sometimes, nonmedical approaches for managing anxiety—such as breathing relaxation, guided imagery, hypnosis, yoga and exercise, and other coping strategies—can be as effective as medications, Dr. Rashid said. She talks to her patients about changing their lifestyles and encourages them to eat frequent meals that provide essential nutrition, to exercise regularly, and to get proper rest. Proper rest and nutrition improve patients’ ability to think and follow guidelines. Eating healthy gives patients more energy and reduces fatigue, which can reduce their stress and associated anxiety.

Patients with cancer, and even cancer survivors, are never completely free from anxiety. Dr. Rashid said, “They feel as though the word is
always hanging over their heads—
the cancer may come back.” However,
about 3 months after diagnosis, once
patients understand the extent of
their disease and the treatment
plan, acute anxiety usually abates.
Unfortunately, for some patients,
depression may then set in.

Depression

Signs of depression include trouble
sleeping, eating too much or too little,
feelings of hopelessness or helplessness,
loss of interest in life, feelings of guilt,
lack of energy, and poor concentration
and memory. Many of the same medi-
cations used to treat anxiety are also pre-
scribed to control depression.

Some of these medications, such as
selective serotonin reuptake inhibitors,
may take 3–4 weeks to become effec-
tive. In the meantime, Dr. Rashid and
the other psychiatrists in the Depart-
ment of Psychiatry support patients
with faster acting medications to con-
trol symptoms and with psychotherapy.

During therapy sessions, the psychia-
trists work to make a connection with
the patient.

According to Dr. Rashid, making
a connection and commitment to their
therapists may keep patients from ac-
ting on suicidal impulses. “The therapist
should collaborate with the patient,”
she said. “My patients make an agree-
ment with me that they will not com-
mit suicide, and if they feel suicidal,
they have multiple coping strategies.”
Sometimes, the therapist will ask the
patient to fill a shoebox with pictures
and mementos of good memories. When
the patient feels very depressed, he or
she can take out the shoebox and look
through it. Making a list of coping
strategies, such as walking the dog or
listening to music, can also work for
some patients. Dr. Rashid added that
asking patients about suicide does not
put suicidal thoughts into their minds;
the question should be asked to deter-
mine what kinds of support patients
need.

Patients with severe depression can
develop psychotic features: Dr. Rashid
recalled having a patient who was so
depressed that the patient believed she
was dead. She had this belief for almost
3 months.

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Obstacles to treatment

Although only about 5% of patients
who are diagnosed with cancer-related
anxiety or depression have a preexisting
psychiatric diagnosis, therapists find it
worthwhile to ask patients about any
past psychiatric problems, including
psychiatric hospitalizations and history
of suicide in the family. “I always ask,
‘How was your childhood?’” Dr. Rashid
said. “A person’s internal reserve can
be depleted by childhood trauma, in-
cluding sexual or physical abuse, and
about 50% of women who were sexually
abused develop depression.”

For cancer patients with advanced
disease, depression, anxiety, and pain
are treated more aggressively. Methyl-
phenidate can also be used to treat
depression and related fatigue in these
patients. Dr. Rashid said that physicians
should not worry about prescribing
higher doses of these medications for
patients with advanced disease because
controlling symptoms is the main con-
cern at the end of life.

“If we can bring the joy back in
somebody’s life, or at least help the
patient live his or her life instead of
having a gloomy existence, then we
have accomplished our goal,” Dr.
Rashid said. “Even though a person
has cancer, life is still worth living.”

FOR MORE INFORMATION
Dr. Anis Rashid .....................713-792-7546

www.mdanderson.org/oncolog
New Antibody Treatment Produces Responses in Patients with Advanced Cancer

A novel antibody treatment produced both tumor regression and disease stabilization in patients with a variety of advanced cancers in a recent phase I clinical trial.

In this multicenter trial, patients who had experienced disease progression after standard systemic therapy for advanced or metastatic cancer were treated with an antibody against the programmed death ligand 1 (PD-L1) protein. The anti–PD-L1 monoclonal antibody was given as an intravenous infusion every 14 days in 6-week cycles for up to 16 cycles.

These results indicate that the anti–PD-L1 antibody could be a safe and useful immunotherapy against a variety of advanced cancers.

The new antibody produced complete or partial tumor responses in 17 of 135 evaluable patients: 9 with melanoma, 5 with non–small cell lung cancer, 2 with kidney cancer, and 1 with ovarian cancer. And 8 patients had responses lasting 12 months or longer. These results were consistent with preclinical studies that indicated the anti–PD-L1 antibody enhances the immune cells' ability to destroy tumors.

The programmed death 1 (PD-1) protein is a T cell co-inhibitory molecule whose ligand, PD-L1, can be overexpressed in certain cancer cells. PD-L1 expression in cancer cells allows them to evade destruction by T cells. The new antibody therapy targets PD-L1 and inhibits its interaction with PD-1, thus enhancing antitumor immunity by allowing activated T cells to destroy the cancer cells.

Although other monoclonal antibodies targeting immune checkpoints have been previously tested, the anti–PD-L1 antibody had fewer and less severe adverse effects. Furthermore, the non–small cell lung cancer responses to the anti–PD-L1 antibody were unexpected because, unlike melanoma or kidney cancer, non–small cell lung cancer typically is unresponsive to immunotherapy. The durability of the responses in multiple tumor types was also unusual.

Taken together, these results indicate that the anti–PD-L1 antibody could be a safe and useful immunotherapy against a variety of advanced cancers. A new phase I trial under way at The University of Texas MD Anderson Cancer Center and other institutions is enrolling patients with refractory breast cancer and gastric cancer in addition to those with the cancer types treated in this study.

The study's report was published in the June 2 issue of the New England Journal of Medicine.

Accelerated Partial-Breast Brachytherapy Associated with Decreased Long-Term Breast Preservation and Increased Complications Compared with Whole-Breast Irradiation

Compared with standard whole-breast irradiation (WBI), accelerated partial-breast irradiation (APBI) in the form of brachytherapy is associated with a decreased likelihood of long-term breast preservation, according to a recent study.

In this retrospective study, researchers at MD Anderson analyzed Medicare claims data from 2003 to 2007 from 92,735 women nationwide who were 67 years or older and had been diagnosed with invasive breast cancer and treated with lumpectomy followed by radiation therapy.

Compared with patients treated with WBI, patients treated with brachytherapy had higher rates of subsequent mastectomy (2.18% and 3.95%, respectively) and complications such as soft tissue infection, hemorrhage, nonhealing surgical wounds, rib fracture, and fat necrosis. Of the complications analyzed, only pneumonitis occurred more often in patients who had received WBI.

“We found that women treated with APBI had about twice the rate of subsequent mastectomy, most likely because of tumor recurrence or local complications, as well as higher rates of postoperative and radiation-related complications,” said Benjamin Smith, M.D., an assistant professor in the Department of Radiation Oncology and corresponding author of the study's report, which was published in the May 2012 issue of Journal of the American Medical Association.

Dr. Smith pointed out that although these differences were significant, both techniques were associated with low rates of local recurrence. He said this retrospective study was important because previous studies had not compared clinical outcomes of the two techniques in older patients. Long-term data from prospective trials of the two techniques will not be available for several years.

One such study already under way at MD Anderson and other institutions is a randomized clinical trial in which treatment outcomes and effects of APBI will be compared with those of WBI in patients 18 years and older.
Cancer Treatment Myths

Misconceptions can be dangerous

Cancer treatment can be a frightening prospect for someone who has just received a cancer diagnosis.

Adding to the anxiety is a confusing mixture of information, some of which is outdated or false. The following are some common myths about cancer treatment and the real facts of the matter.

**MYTH:** Cancer treatment side effects are worse than the disease.

**FACT:** Although cancer treatments such as chemotherapy and radiation can have unpleasant side effects, recent advances in antinausea medications, precision radiation treatments, and minimally invasive surgery have greatly diminished patients’ discomfort. Today, side effects such as nausea, vomiting, and tissue damage are less severe than in the past.

Oncologists meet with each patient and family to set goals for effective control of the cancer and maximization of the patient’s quality of life during and after treatment.

**MYTH:** Cancer is always painful.

**FACT:** Some cancers never cause pain. For patients who do experience pain, especially those with advanced cancer, doctors today strive to recognize the need to control the pain and have better ways to manage it. These include the use of pain medications, treatments to shrink or remove pain-causing tumors, and interventional pain procedures such as epidural injections and nerve blocks.

Although all pain may not be completely eliminated, it can be controlled so that it has the least possible impact on a patient’s function and well-being.

**MYTH:** Cancer treatment means being confined to a hospital bed.

**FACT:** Most people are treated for cancer on an outpatient basis, and hospital stays, when necessary, are much shorter than in past decades. Often, oncologists at cancer centers work with doctors in patients’ hometowns to provide continued care there, allowing patients to be with family and friends and continue their daily activities during cancer treatment.

**MYTH:** Everyone with the same kind of cancer receives the same kind of treatment.

**FACT:** Physicians now tailor cancer treatment to the individual patient. The kind of treatment received is based on where the cancer is located, whether or how much it has spread, and how it affects body functions and general health.

In addition, a patient’s overall health affects the choice of treatment. Increasingly, the gene mutations present in a patient’s cancer also are helping guide the type of treatment.

**MYTH:** Positive thinking will cure cancer.

**FACT:** There is no scientific evidence that a “positive attitude” provides patients with an advantage in cancer treatment or improves their chance of being cured. However, it is important for patients to stay active, maintain relationships with family and friends, and continue enjoyable activities.

**MYTH:** Some people are too old for cancer treatment.

**FACT:** There is no age limit for cancer treatment, which can be just as beneficial for older adults as for younger ones. More important than a patient’s chronological age is the body’s biologic age. Cancer patients who are older but have no other serious illness, such as heart disease or diabetes, often do as well as or better than younger patients with additional health issues. People with cancer should receive the treatment that is best suited to their condition and overall health, irrespective of age.

**MYTH:** A needle biopsy can cause cancer cells to spread to other parts of the body.

**FACT:** A needle biopsy is a procedure done to learn what kind of tumor a patient has. In this procedure, a needle is inserted into the tumor to remove a bit of tissue, which is then studied under a microscope. For most types of cancer, there is no evidence that performing a needle biopsy can influence metastasis to other parts of the body.

There are exceptions. For example, testicular cancer is not diagnosed using a needle biopsy of the testicle. Instead, blood tests and imaging techniques such as ultrasonography are used, and if a doctor suspects testicular cancer, the testicle is removed at some point in the course of treatment.

**MYTH:** Exposing a tumor to air during surgery causes cancer to spread.

**FACT:** Surgery can’t cause cancer to spread. Surgically removing cancer is often the first and most important treatment.

**MYTH:** Cancer is an incurable disease, and going for treatment is pointless.

**FACT:** With the medical advances made in recent years, the death rate from cancer has greatly decreased. Several forms of cancers are now curable. In other types, effective treatments have extended patients’ lives for many years after their initial diagnosis.

There are many types of cancer and numerous treatments, so stories about a particular patient’s experience will not apply to others. Doctors and nurses are the most reliable source of information for cancer patients.

— K. Stuyck

FOR MORE INFORMATION

- Talk to your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
Circulating Tumor Cells Have Predictive Value in Early-Stage Breast Cancer

Circulating tumor cells (CTCs)—cancer cells detectable in the blood—are known to predict disease progression in patients with metastatic breast cancer. And CTCs have now been shown to predict post-therapy relapse in patients with early-stage breast cancer.

In a prospective study, researchers at The University of Texas MD Anderson Cancer Center collected blood samples from 302 patients just before definitive surgery for stage I, II, or III breast cancer. None of the patients had undergone pre-operative chemotherapy; about two-thirds of the patients received postoperative chemotherapy. The mean age of patients enrolled in the study was 54 years; the median follow-up time was 35 months.

The CTCs were measured in the blood samples using the Veridex CellSearch System and reported as the number of CTCs/7.5 mL blood. The researchers found one or more CTCs in samples from 73 patients (24%); 29 patients (10%) had two or more CTCs, and 16 (5%) had three or more.

Detection of one or more CTCs predicted decreased rates of 2-year progression-free survival. Eleven (15%) of the 73 patients with one or more CTCs experienced a cancer relapse, compared with 7 (3%) of the 229 patients with no CTCs. An increased number of CTCs was also associated with lower rates of overall survival. At 2 years, the overall survival rates for patients with one or more, two or more, and three or more CTCs were 94%, 89%, and 81%, respectively, compared with a 99% rate for patients with no CTCs.

“There are a significant number of nonmetastatic breast cancer patients for whom you remove their tumor, take out the lymph nodes, treat them with systemic therapy, and render them free of any evidence of disease. However, around 2 years later—a peak time for recurrence—25%–35% of those women will have evidence of metastatic disease, and we wanted to understand why,” said principal investigator Anthony Lucci, M.D., a professor in the Department of Surgical Oncology.

Dr. Lucci said the results of the study, which were published in *Lancet Oncology*, will need to be validated by a larger study before they can affect clinical decision making about systemic therapy in early-stage cancer patients.

“25%–35% of those women will have evidence of metastatic disease, and we wanted to understand why.”

– Dr. Anthony Lucci