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*Making Cancer History**

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REPORT TO PHYSICIANS

SEPTEMBER 2006 Vol. 51, No. 9

OncoLog



Like many patients with liver tumors, [REDACTED] had run out of options. Then Sunil Krishnan, M.D., an assistant professor in the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center, offered him a chance to enroll in a pilot study of image-guided radiation therapy using implanted gold fiducial markers to track the liver's precise location.

"My doctor recommended it, and I don't have anything to lose," [REDACTED] said. "I mean, I have cancer, so I've got to do something. If they can help me and extend my life, I'm all for it."

[REDACTED] is the fourth patient to be treated on the pilot study, which uses four-dimensional (4-D) computed tomography (CT) treatment planning and respiratory gating to tackle the

Zeroing In on a Moving Target

New four-dimensional imaging techniques show impressive accuracy in pinpointing liver tumors for radiation therapy.

by Dawn Chalaire

Dr. Krishnan (l) and Kim Tran, radiation therapist, position [REDACTED] for treatment.

problem of liver tumor movement during breathing. So far, this method of treatment delivery has shown astounding accuracy in pinpointing the location of liver tumors. Investigators hope that by perfecting the art of hitting a moving target, they will be able to deliver higher doses of radiation with less damage to normal liver tissues.

Liver tumors are relatively rare in the United States, but their incidence is

(Continued on next page)

THE UNIVERSITY OF TEXAS
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Zeroing In on a Moving Target

(Continued from page 1)

rising, mainly because of an increase in hepatitis B and C infections. Treatment for primary (mainly hepatocellular carcinoma) and metastatic liver tumors is largely ineffective. Liver transplantation has the highest 5-year survival rate (50% to 71%), but it is limited by a shortage of livers for transplant. Among other treatments, surgery is the most effective, with a 5-year survival rate of 31% to 56%. However, fewer than 15% of patients with hepatocellular carcinoma are candidates for surgery or transplantation.

The remaining 85% of patients with unresectable liver tumors have few potentially curative treatment options. Systemic chemotherapy results in response rates of less than 20% and has no effect on survival. Treatment with locally ablative therapies, such as percutaneous ethanol injection and radiofrequency ablation, can be successful, but only in tumors smaller than 5 cm.

For many years, radiation therapy was not considered a viable option for treating liver tumors because the maximum tolerated dose for whole-liver irradiation, 30 Gy, is much lower than therapeutic levels.

Although the liver has the ability to regenerate after resection, it is unable to do so after radiation therapy and is easily damaged by radiation. Also, radiation-induced liver disease can occur if too much of the normal liver tissues are irradiated.

More precise imaging techniques

The outlook for the treatment of liver tumors with radiation began to change in the early 1980s when radiation oncologists started using three-dimensional conformal and intensity-

modulated radiation therapy to escalate the dose to liver tumors focally and limit the dose to normal liver tissue. This shift toward more targeted radiation therapy has been made possible by more precise imaging techniques, including three-dimensional CT. The standard imaging technique used for conformal radiation therapy is to take simulation CT scans for treatment planning a few days before radiation is delivered. Marks made on the patient's body are aligned with the internal anatomy and treatment beams. Then, marks on the patient's body are aligned with lasers in the radiation treatment

entire estimated range of motion, plus a wide margin, which resulted in exposure of a large volume of normal liver tissue to radiation.

Refining the state-of-the-art

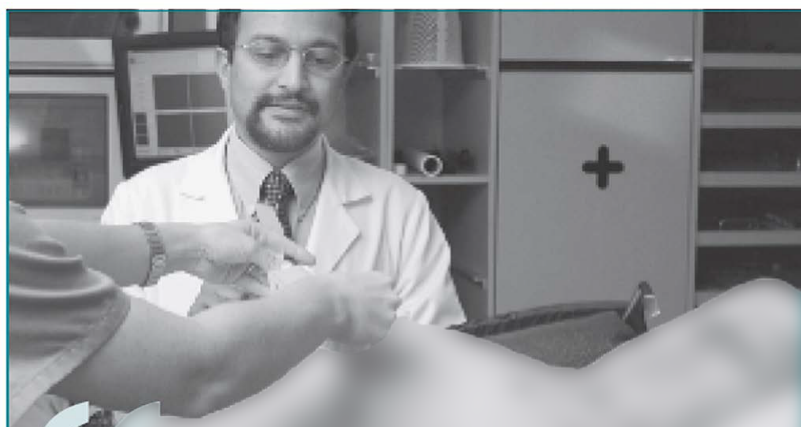
Today, 4-D CT, which involves taking CT scans of the tumor at each of 10 designated phases in the respiration cycle, is the standard of care for radiation treatment planning at M. D. Anderson, but investigators are working to improve the accuracy even further. In a pilot study initiated by Dr. Krishnan and his colleagues Drs. Sam Beddar and

Tina Briere in the Department of Radiation Physics, 4-D CT is being combined with intravenous contrast to obtain pretreatment images of the liver during the entire respiratory cycle. "I think we're the only group in the country that is routinely using 4-D scanning with intravenous contrast for imaging liver tumors," Dr. Krishnan said.

Once 4-D CT scans are obtained, the standard approach is to define an internal treatment volume that encompasses the tumor in all 10 phases of the respiratory cycle. Treatment is then delivered via three-dimensional conformal or intensity-

modulated radiation therapy. Although this technique is state of the art, Dr. Krishnan and his colleagues are working to refine it. In their pilot study, they are using a different technique to account for intrafraction motion—respiratory gating.

In gated radiation therapy, the linear accelerator is triggered to begin delivering radiation at a specific point in the respiratory cycle. At another specified point, radiation delivery is halted. In standard gated treatment delivery, a small box is placed on the patient's stomach as a standard of reference,



I think we're the only group in the country that is routinely using 4-D scanning with intravenous contrast for imaging liver tumors."

– Dr. Krishnan

room to reproduce the positioning during simulation.

"This works really well for static tumors," Dr. Krishnan said, "but the liver is assumed to have an up and down motion due to breathing."

This type of organ motion during radiation treatment delivery, which is known as intrafraction movement, can cause the radiation beam to miss its target. Twenty years ago, radiation oncologists accounted for the intrafraction movement of liver tumors by expanding the treatment margin around the tumor to encompass the

and its location throughout respiration is recorded by a camera. The motion of the box, or external fiducial, is used to track the motion of the tumor internally, but there is no guarantee that the correlation between the external fiducial and the tumor is consistent. The two objects move differently, and that, combined with residual movement of the tumor during gating, can cause significant errors in treatment delivery. "The box is an external surrogate for what's going on inside, but we felt that an internal surrogate would be more accurate," Dr. Krishnan said.

To track the movement of the tumor internally, investigators are using three gold fiducials implanted inside the liver. In consultation with Dr. Krishnan, Ravi Murthy, M.D., an associate professor in the Department of Diagnostic Radiology, inserts the fiducials, spacing them three-dimensionally 2 to 3 cm apart, preferably outside the tumor itself. After the fiducials have had 2 to 3 days to settle into their permanent positions in the liver, 4-D CT with intravenous contrast is used to obtain treatment-planning images. The patient is then taken to the combined CT-linear accelerator treatment room, where an electronic portal imaging device is used

to test whether the external fiducial consistently tracks the movement of the internal fiducials. If a reliable correlation cannot be found, the patient will receive 4-D CT-based conventional radiation therapy.

"So far, though, the study results have far exceeded our expectations of how accurate we could be," said Dr. Krishnan. "The positioning accuracy is unparalleled. For a moving target, 2- to 3-mm accuracy is an amazing degree of accuracy."

The study, which is still open and accruing patients, is designed for people with liver tumors larger than 4 cm and no extrahepatic disease. Dr. Krishnan pointed out that a larger, prospective, multi-institutional study will be needed to measure outcomes of the experimental treatment. He hopes that the combination of 4-D CT-based gated radiation therapy and stereotactic radiation therapy techniques will reduce the number of treatment fractions in standard photon therapy for liver tumors from about 30 to 5. He also is optimistic that the techniques used in the current pilot study can be applied to proton therapy. ●

FOR MORE INFORMATION, contact Dr. Krishnan at (713) 563-2377.

Fifth International Meeting on Hepatocellular Carcinoma

January 11-13, 2007

The University of Texas

M. D. Anderson Cancer Center

Robert C. Hickey Auditorium

11th Floor, R. Lee Clark Clinic

This conference will review and discuss state-of-the-art multidisciplinary treatment of patients with hepatocellular carcinoma. Innovative strategies for diagnosis and treatment will be emphasized, including surgical and non-surgical treatment and transplantation. The conference will be beneficial for surgeons, gastroenterologists, medical oncologists, radiologists, radiation oncologists, physician assistants, and nurses involved in the research and care of patients with liver cancer.

Participants can earn up to 15.00 AMA PRA Category 1 Credits for continuing medical education.

Deadline for advance registration is Dec. 22. For more information, visit www.mdanderson.org/conferences online, or email the Department of CME/Conference Services at register@mdanderson.org.

RADIATION PROTOCOLS

- Pilot study of image-guided radiation therapy using implanted fiducial markers in hepatobiliary tumors (2005-0024). Physician: Sunil Krishnan, M.D.
- Phase II stereotactic body radiotherapy for stage I (T1-T2, N0, M0), selective stage II (chest wall T3, N0M0), or isolated peripheral lung recurrent non-small cell lung cancer (2005-0574). Physician: Joe Y. Chang, M.D., Ph.D.
- Assessing the magnitude and potential impact of respiration-induced 3-dimensional motion of tumors and normal tissues using 4-dimensional CT technology (2003-0962). Physician: James D. Cox, M.D.
- Image-guided adaptive intensity-modulated radiation therapy for head and neck cancer (2004-0064). Physician: Adam S. Garden, M.D.
- Assessment of the reliability of implanted fiducials for tracking of respiratory-induced tumor motion (ID03-0208). Physician: George Starkschall, Ph.D.
- Phase II trial comparing 4-dimensional CT-derived ventilation versus SPECT/CT Tc-99m aerosol ventilation in patients with lung cancer (2006-0698). Physician: Thomas M. Guerrero, M.D., Ph.D.

FOR MORE INFORMATION, visit www.clinicaltrials.org, or call (800) 392-1611 or (713) 792-3245.

New Life for an Old Drug

Thalidomide—and its newer, better tolerated derivatives—is back, and it’s making a better name for itself this time as a promising treatment for several kinds of cancer.

by Angelique Siy

Thalidomide became infamous worldwide for causing thousands of serious birth defects in the late 1950s and early 1960s. But in the years since it was pulled from the market, researchers have found new ways to capitalize on its properties—some of which are inseparable from the ones that gave the drug its bad reputation.

In recent years, thalidomide has been shown to be successful in treating erythema nodosum related to leprosy as well as some hematologic cancers, such as myelodysplastic syndrome (MDS) and multiple myeloma. In fact, thalidomide led researchers to discover an entire class of promising related drugs: IMiDs, or immunomodulatory agents, which along with other novel agents, have revolutionized the treatment of multiple myeloma. One of the IMiDs, lenalidomide (Revlimid), performed so well in trial after trial that it was licensed for use in multiple myeloma and one form of MDS within 6 years of entering clinical trials. Lenalidomide is more potent against cell lines and has a different toxicity profile than thalidomide—in particular, it does not appear to have the teratogenic effects that led to thalidomide’s downfall.

The way IMiDs modify or regulate the functioning of the immune system is not known, but they have been documented as effective anti-angiogenics and anti-inflammatories, with direct cytotoxic effects on myeloma cells—both in vitro and in patient-derived primary myeloma cells—and some effects on the microenvironment of the bone marrow that affects myeloma cell growth. In addition to being anti-angiogenic, lenalidomide seems to affect myeloma cells by inducing apoptosis, inhibiting growth, and reducing adhesion to bone marrow stromal cells. Clinical investigators have realized that other IMiDs share these traits to different degrees and with

different adverse effects, which they hope means that less toxic and more effective drug combinations can be discovered. Trials of IMiDs given in combination with other proven antimyeloma agents such as bortezomib, a proteasome inhibitor, and other chemotherapeutics like cyclophosphamide, melphalan, dexamethasone, and doxorubicin have provided alternative and improved regimens for myeloma. Future studies with biphosphonates (pamidronate and zoledronic acid), an anti-CD40 monoclonal antibody, and even the “proto-IMiD,” thalidomide, may provide even more options for patients with this multiple myeloma.

Donna Weber, M.D., who has been involved in multiple myeloma clinical research, is an associate professor in the Department of Lymphoma at The University of Texas M. D. Anderson Cancer Center. “We are finding more and more active novel agents. With thalidomide, lenalidomide, and bortezomib, there is additive, and probably synergistic, interaction, so that even if patients are resistant to these drugs as single agents, they can be combined with each other, as well as with conventional agents, providing many more effective alternative combinations for the treatment of myeloma.

“The IMiDs are unique; there’s an entire range of possibilities with them,” Dr. Weber continued. “The old and new agents are being used together in the same regimens. Each novel agent has shown survival benefits. It’s a whole new world for myeloma patients. I’ll give you an example of the impact it has had on just one patient.”

Good timing pays off

“In 1992, I had a patient who was diagnosed with multiple myeloma,” Dr. Weber said. “The standard of care in



“For the field of myeloma, finding a new single agent whose activity is nearly as great as steroids is monumental.”

— Dr. Donna Weber

1992 was essentially combinations of alkylating agents or anthracyclines, like melphalan and prednisone, or vincristine, Adriamycin, dexamethasone (VAD), followed by myeloablative therapy with stem cell transplant. When these and other treatment options began to fail in slowing the disease, we tried intensive therapy supported by autologous hematopoietic stem cell transplantation. When that also failed and we couldn’t find a match for an allogeneic transplant, the patient was running out of options.

“That’s when (1997) Dr. Bart Barlogie’s initial findings of thalidomide’s apparent effectiveness against multiple myeloma were reported at the International Myeloma Workshop,”

said Dr. Weber. “Fortunately, we were among the first to begin trials to confirm its efficacy. This patient did well on thalidomide, and subsequent thalidomide combinations controlled the disease until about 2 years ago. By that time the field of myeloma was in a new phase of discovery and we were able to try another new agent, bortezomib.” Bortezomib (Velcade) is one of a new class of drugs called proteasome inhibitors and was approved by the FDA for resistant multiple myeloma in May 2003.

And the patient? “He achieved his best response ever, a complete remission, on bortezomib,” said Dr. Weber.

That patient was far from alone in having so few treatment choices against so lethal a cancer. Multiple myeloma, also called myeloma or plasma cell myeloma, accounts for 13% to 33% of all hematologic cancers and affects 50,000 people in the U.S. alone. A patient diagnosed with multiple myeloma is typically 65-75 years old and faces a mean survival time of 3 to 5 years. The disease’s 5-year survival rate of 32% has remained virtually unchanged for over 45 years. Although relapses are common, nearly half the patients diagnosed with multiple myeloma will, as a result of these new treatments, achieve complete remission, and with time many doctors expect to see the benefit of novel agents in terms of survival.

Treatment breakthroughs

Now, with the approval of thalidomide, bortezomib, and lenalidomide for multiple myeloma, there is a whole new treatment paradigm for multiple myeloma. Lenalidomide’s potential would not likely have been discovered had it not piggybacked on thalidomide’s rediscovery. Fortunately, several very persistent and innovative thinkers, over the course of 30 years, connected the ideas that angiogenesis might be important to the growth and spread of cancer; that thalidomide was possibly anti-angiogenic; and that multiple myeloma, a disease for which treatment progress was slow, might respond to anti-angiogenic treatment, given that the bone marrow of patients with multiple myeloma had been shown to have significant vascularization. This was followed by the realization that

IMiDs had many other effects on processes that drive myeloma cell growth.

By the early 2000s, Dr. Weber and colleagues had completed several studies that confirmed and expanded upon the results of Dr. Barlogie’s (University of Arkansas for Medical Sciences [UAMS] in Little Rock, Arkansas) original thalidomide trial in patients with advanced multiple myeloma.

Dr. Weber recalls a series of discoveries that led to a great deal of attention: “After the original thalidomide discovery, it was kind of a fluke that we gave one-tenth the standard myeloma dose of dexamethasone to treat a rash in a patient with VAD-resistant disease being treated with thalidomide. The patient went into remission and this led to an observation that 45% of patients responded to the combination of thalidomide and dexamethasone despite prior resistance to both drugs given as single agents. This opened the door for many new combinations for novel and established agents for treatment of myeloma. In August 2001, the UAMS lead researcher told the American Cancer Society that because preliminary studies of thalidomide were so promising, many oncologists weren’t waiting; they were using it off-label in patients whose cancer had failed to respond to other therapies. He estimated that about 10,000 patients worldwide with multiple myeloma had received the drug, which meant there was much more evidence to publish.

“After that, many trials confirmed the initial findings for resistant myeloma. It was very exciting because of the dramatic results for resistant disease, and it was natural for investigation to expand to untreated patients with myeloma. Two concomitant trials (M. D. Anderson, Mayo Clinic) demonstrated 65% to 70% response rates in previously untreated patients with potentially serious but manageable side effects, which led to a 2001 randomized trial that confirmed thalidomide and dexamethasone’s superiority compared with dexamethasone alone and subsequent approval of thalidomide in 2004 for use in treating previously untreated myeloma patients.

“For the field of myeloma, finding a new single agent whose activity is nearly as great as steroids is monumental,” Dr. Weber said. “When thalidomide made its reappearance, it changed a lot

of patients’ lives. Myeloma became the field to watch, and in the last decade, three new novel agents have been approved. The growth of the field has been amazing.”

In 2000, phase I and II clinical trials demonstrated activity of lenalidomide in myeloma patients. Dr. Weber and her team were the national principal investigators, and two trials proved lenalidomide had a manageable adverse effect profile. At high doses, lenalidomide’s most common toxicities included thrombocytopenia, neutropenia, and skin rash. Based on these results, the FDA awarded the drug a fast track designation for relapsed and refractory myeloma in February 2003.

Dr. Weber and her team were the investigators for a North American phase III trial that proved superiority of lenalidomide-dexamethasone over dexamethasone alone for patients with relapsed multiple myeloma. The results of this trial were nearly identical to a concomitant sister trial in Europe, Australia, and Israel led by Dr. Meletios Dimopoulos. By March 2005, these two ongoing phase III clinical trials demonstrated lenalidomide-dexamethasone to be more effective than dexamethasone alone. The trials were unblinded early, and patients who had not been given lenalidomide were given the option of adding it to their regimen, if warranted. In June of this year, lenalidomide received FDA approval for use in combination with dexamethasone as a treatment for patients with multiple myeloma who have received at least one prior therapy.

And next?

Dr. Weber suspects the advances will continue. “As the novel agents help translational scientists unravel the basic mechanisms of the plasma cell and its microenvironment, it may be possible to develop new agents to attack these novel pathways and to learn more about the development of resistance to treatment and how to avoid it,” she said. “It has been an amazing decade for this disease. There has been a revolution in the field providing a promising future for patients with myeloma.”

FOR MORE INFORMATION, contact Dr. Weber at (713) 792-2850.

Drug Combination Promising for Metastatic Prostate Cancer

M. D. Anderson scientists previously showed that the use of a combination of imatinib (Gleevec) and paclitaxel (Taxol) to block platelet-derived growth factor receptors (PDGF-R) in an extremely drug-resistant mouse model of metastatic prostate cancer effectively reduced the size of tumors and cut the incidence of metastasis. In a follow-up study, published in the June 7 issue of the *Journal of the National Cancer Institute*, the researchers examined whether the combined agents worked by attacking tumor cells or tumor-related blood vessels. They found that tumor-associated endothelial cells seemed to be the target for imatinib and chemotherapy, rather than the tumor cells.

When imatinib and paclitaxel were administered in combination to mice with a multiple-drug-resistant form of prostate cancer, the incidence of bone metastases and the size of tumors were significantly reduced. Tumors were found in only 4 of 18 mice treated with the combination, median tumor weight was one-tenth of a gram, and the cancer spread to the lymph nodes in three mice. By comparison, tumors grew in all 19 control mice, the median tumor weight was 1.3 grams, and all mice had lymph node metastasis.

Isaiah J. Fidler, Ph.D., chair of the Department of Cancer Biology and director of the Cancer Metastasis Research Center at M. D. Anderson, and colleagues showed that imatinib inhibited phosphorylation of PDGF-R in tumor-associated endothelial cells, rendering these cells sensitive to apoptosis mediated by chemotherapy. The death of blood vessel cells led to the death of surrounding tumor cells.

Dr. Fidler said these findings are a vibrant example of the “seed and soil” hypothesis in metastasis—that when metastatic cells enter the circulation, most die off quickly and the cells that survive do so because they find a microenvironment specifically conducive to their growth. For prostate cancer, that’s bone. “Here, we attack the

endothelial cells themselves, and killing the vasculature prevents survival of the tumor cells,” he explained.

Based on these promising laboratory results, researchers at M. D. Anderson are now leading a phase II clinical trial testing imatinib and docetaxel (which is in the same family of drugs as paclitaxel) in androgen-independent prostate cancer.

Chronic Stress Promotes Ovarian Tumor Growth

Many people believe that a connection exists between high levels of stress and cancer, but there has been little scientific proof until now. In the August issue of the journal *Nature Medicine*, M. D. Anderson researchers have shown the first measurable link between psychological stress and the biological processes that make ovarian tumors grow and spread.

“The concept of stress hormone receptors directly driving cancer growth is very new... Our research opens a new area of investigation.”

– Dr. Sood

When the researchers induced chronic stress in mice with ovarian cancer, the tumors of the mice grew and spread more quickly. “This study provides a new understanding of how chronic stress and stress factors drive tumor growth,” said Anil Sood, M.D., professor of gynecologic oncology and cancer biology and director of ovarian cancer research.

“The concept of stress hormone receptors directly driving cancer growth is very new,” said Dr. Sood, the study’s senior author. “Not much had been known about how often these receptors are expressed in cancer, and more importantly, whether they had any functional significance. Our research opens a new area of investigation.”

The research began when Dr. Sood and his colleague, Susan Lutgendorf, found an association between ovarian cancer patients who reported high levels of distress in their lives and an increase in the β_2 adrenergic receptor that stimulates blood vessel growth in tumors. By contrast, patients who reported more social support in their lives had lower levels of this factor. Dr. Sood wondered if hormones associated with chronic stress might affect how cancers grow.

Dr. Sood’s research team developed a mouse model of ovarian cancer to study the link. The researchers confined the mice in a small space for zero, 2, or 6 hours during the day, which caused the mice to produce the same stress hormones humans produce under stress.

Dr. Sood and his colleagues found that, surprisingly, cancer cells make receptors for these hormones on their surface and that when these receptors are activated they set in motion a chain of events that leads to angiogenesis, allowing tumors to grow and spread more rapidly.

After 3 weeks, the researchers measured the number and size of tumors in the mice. The number of tumors was 2.5 times greater in the mice that had been in the 2-hour stress group and 3.6 times greater in the 6-hour stress group compared with the mice with no stress. In addition, tumor growth was confined in the no-stress mice but had spread to the liver or spleen in half of the stressed mice.

Researchers also found that when they blocked the stress hormone receptors in their experimental system using the beta blocker propranolol, they also stopped the negative effects of stress on tumor growth. “The medication neutralized the effect of stress on tumor growth,” said Dr. Sood.

“Beta blockers have been shown to be protective against cardiac disease,” he said. “No one has studied their effect on chronic stress as it relates to cancer in humans. There is a lot of interest now in this area of combining behavioral interventions to reduce stress, as well as looking at the use of beta blockers in cancer patients.”



Managing Your Medications



If you must take several prescription drugs each day, taking the medicine correctly can be a challenge. For instance, some cancer patients take more than 20 medications a day, each with its own special instructions and side effects.

Finding the right system to organize those medicines can go a long way toward protecting your health and creating order out of chaos.

Questions to ask your doctor

Organizing starts with getting the correct medical information. You should ask your physician about each drug being prescribed: What is the name and purpose of the drug and why are you taking it? When should you take it and for how long? When should you expect to see a benefit? What kind of side effects does it have, and are there any you should report to the doctor immediately? Write down the answers to the questions so you'll remember them. Your pharmacist also can provide valuable information about your medications, and many pharmacies provide helpful print outs about your prescriptions for reference later.

Keeping a record of your medications

After that, it's time to make a record of what you're taking. Julie Corwin, program coordinator in M. D. Anderson Cancer Center's Department of Employee Health and Well-being, advises, "It's a good idea to keep a record of your medications, including the name and strength of the medication, the color of the pill, what you are taking it for, when you began taking it, dosage instructions, and any food or drug interactions." It's also important, she said, to keep track of (and discuss with your doctor) any over-the-counter medication or vitamin and herbal supplements you're taking. Some of these can interact with your prescription medica-

tion and possibly even interfere with their effectiveness. This record should also include basic information such as your name, home and work phone numbers, blood type, medical conditions, emergency contact information, your doctor's name and phone number, and a list of any food or drug allergies.

Ways to organize your medications

There are a variety of systems that can help you remember when to take your medications.

- **Pill organizers are one simple solution.** These containers, available in different shapes and sizes at drug stores, provide spaces for the pills to be taken on each day of the week and, in some versions, also at different times of the day. Some have child locks, built-in reminder alarms, and automatic pill dispensers. There are also an assortment of alarms and watches that signal you when it's time to take medication.

- **You can create your own organizer** by putting each day's pills in a small cup or two cups if you take some medications in the morning and some later in the day. If you must take an assortment of pills at various times throughout the day, an empty egg carton can be an effective organizer. Number the 12 sections of the carton for 12 hours of the day. Then place the medication you need to take at that time in the proper container. At 3 p.m., for instance, you'd take the pills in section number three.

- **Charts and calendars are other options.** One method involves writing your drug schedule on a calendar. Then, each time you take that day's dosage, cross it out on the calendar. Another idea is to use different-colored stickers on the lids of each medicine bottle. Every time you take the medicine, you place a sticker of the same color on the calendar as a visual reminder of which pills you've taken. New York State's Office for the Aging offers several helpful medicine charts that you can print from their Web site: <http://agingwell.state.ny.us/pharmacy/articles/media01.htm>.

Pick a system that works for you. Organizing your medications can make your life simpler and help you get the most benefit possible from your treatment. ●

If you must take an assortment of pills at various times throughout the day, an empty egg carton can serve as an effective organizer.

For more information, talk to your physician, or:

- call the M. D. Anderson Cancer Center Information Line at (800) 392-1611 (Option 3) within the United States.
- visit www.mdanderson.org.

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K. Stuyck

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Adjuvant Therapy for Aggressive Kidney Cancer

Christopher G. Wood, M.D.
Associate Professor of Urology
and Cancer Biology

Every postoperative visit, the inevitable question comes up, "What can I do to make sure this doesn't come back? I want to be as aggressive as possible!" We tell patients that the vast majority of people with renal cell carcinoma are cured surgically, so we'll watch them closely, but they don't need further therapy.



It's true that relapse is rare, but when it happens, the outcome is usually less than satisfactory. The fact that we currently have no effective adjuvant therapy to decrease the risk further is our Achilles' heel—but researchers are working hard to change that.

Logically, therapies that demonstrate some efficacy in the metastatic setting should have a greater impact at a time of minimal residual disease, but this approach hasn't, thus far, translated into success in renal cell carcinoma. The mainstays of therapy for metastatic disease have shown no benefit in the adjuvant setting. We have, however, learned some important lessons:

- What side effects are patients willing to tolerate for the possible benefit of an experimental therapy? Toxicity versus risk of recurrence becomes the equation that determines what a patient will endure. With a low risk of recurrence, patients are less likely to try a treatment with even modest toxicity.

- The importance of placebo: New therapies are tested against the standard of care, which in this case means doing nothing. Patients who are motivated enough to participate in a clinical trial are usually keen on getting the drug being tested and see a placebo arm as lesser therapy for their disease.

- It may be that the biology of tumor progression and metastasis is completely different in locally advanced disease and therefore requires different treatment approaches. It may be time to change the way we identify potential agents for use in the adjuvant setting.

- Locally advanced renal cell carcinoma is rare, which is a blessing, but it is also a curse for populating clinical trials. I think it's important to target our efforts carefully or risk undermining the clinical trial process. There currently are three adjuvant trials ongoing in the world, all with lofty accrual goals. Probably the most significant of these is the ECOG intergroup ASSURE Trial, which compares one year of sunitinib or sorafenib with placebo after curative nephrectomy. The accrual goal is over 1,300 patients and will require the efforts of everyone treating kidney cancer to complete. There are many promising drugs in the pipeline, but they will have to wait in line for these ongoing trials to finish or we risk diluting our efforts.

Effective adjuvant therapy remains elusive right now, but I believe we are closing in. I look forward to the day when I will be able to tell postoperative patients, "Take this, and it will increase the probability that your kidney cancer will not come back." ●

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