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OncoLog MD Anderson's Report to Physicians

2004

OncoLog Volume 49, Number 12, December 2004

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REPORT TO PHYSICIANS

DECEMBER 2004 Vol. 49, No. 12

Oncology



Dr. Deborah Kuban (l), a professor in the Department of Radiation Oncology, and **Dr. Curtis Pettaway**, an associate professor in the Department of Urology, discuss treatment options at a multidisciplinary conference.

Advances in Prostate Cancer Treatment

From tiny radioisotopic implants that deliver radiation inside the prostate gland to nerve grafts that are helping men retain sexual function after surgery, here's what's new—and what's next—in prostate cancer treatment.

by **David Galloway**

A diagnosis of prostate cancer carries a vastly different meaning for a patient today than it did 15 years ago. These cancers are being detected at earlier stages, and tumor control rates are soaring.

Since the advent of the prostate-specific antigen (PSA) test in the early 1990s, many prostate cancers are being

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Advances in Prostate Cancer Treatment

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treated before they are even palpable on a physical examination. Now, more than half of the patients seen for radiation therapy have been diagnosed at this early stage, said Deborah A. Kuban, M.D., a professor in the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center.

PSA testing has allowed physicians to discover many cases of prostate cancer that might have gone undetected in the past. This led to what appeared to be an increased incidence of prostate cancer in the early 1990s. "It is clear that, through PSA testing and newer, more aggressive biopsy strategies, we certainly find more cancers," said Curtis A. Pettaway, M.D., an associate professor in the Department of Urology at M. D. Anderson.

"And so the question becomes: Are we now finding some cancers that we don't need to find? Perhaps some of the cancers we're finding would never have caused the patient a problem," Dr. Pettaway said.

Paul Mathew, M.D., an assistant professor in the Department of Genitourinary Medical Oncology at M. D. Anderson, cited "a very apt aphorism" by the late Willet Whitmore, Jr., M.D., of Memorial Sloan-Kettering Cancer Center in New York: "If cure is necessary, is it feasible? And if cure is feasible, is it necessary?" Dr. Mathew said that dichotomy frames the current view of localized prostate cancer. A 50-year-old patient with an aggressive type of prostate cancer is almost certain to die of his disease unless it is cured. "It's clearly necessary," he said, "but is it feasible? Do we have clear evidence that radical prostatectomy offers cure in a high-grade prostate cancer? Surprisingly, this is still a controversial area." On the other hand, in an 80-year-old patient with a low-grade cancer, "If you remove his prostate, he'd be cured. But is it really necessary?" Such a patient might well live the rest of his life without experiencing significant problems related to the cancer.

To evaluate those options, a patient's

"With laparoscopy, you can sample the lymph nodes and remove the prostate as completely as you would with an open incision, using five smaller incisions."

– Dr. Curtis Pettaway

risk of treatment failure is assessed on the basis of his PSA level, tumor stage, and combined Gleason score. Patients with a PSA level less than 10, a tumor stage of T2a (a small, palpable tumor confined to the gland) or lower, and a Gleason score of 6 or less are in the low-risk category, with an 80% or greater chance of long-term control. Those with a PSA level higher than 20, a tumor stage of T3 (outside of the gland) or higher, and a Gleason score of 8 or higher are in the high-risk category with less than a 50% chance of long-term control. All those in between are in the intermediate-risk group.

For patients whose life expectancy and comorbidities suggest that they are likely to die of something other than prostate cancer, cure is not considered necessary, so a strategy of watchful waiting is typically chosen. The patient's PSA level is checked every four to six months and, as long as the cancer remains minimal, treatment remains unnecessary.

For younger patients or for those with more aggressive cancers, though, treatment is necessary, and several options are available. "And because, in many patients, we can't truly say that one option is better than the others, it comes down to the patient's decision," Dr. Kuban said.

Radiation options

Although it can be delivered in a nearly endless variety of configurations, radiation therapy comes in two basic forms: internal or external.

External-beam radiation therapy has changed dramatically over the years because of technological improvements in imaging and in the treatment devices themselves. With the rise of computed tomography, sonography, and intensity-modulated radiation therapy (which uses lead blocking devices to shape the beam and delivers the dose from several different angles), it is now possible to deliver a higher dose of radiation to the prostate while sparing the rectum and bladder, minimizing the complications that plagued patients treated for prostate cancer in the past.

Radiation can also be delivered internally through the use of radioisotopic implants. "It's all done through a needle through the perineum, using a grid and using ultrasound ahead of time to map out where we're going to put the needles and where we're going to put the seeds," Dr. Kuban said. The radioactive metallic seeds are smaller than grains of rice, and 80 to 100 of them are typically implanted into a prostate gland. The big advantage from the patient's perspective is that it is a one-time procedure, as opposed to 42 treatments over eight and a half weeks for external-beam therapy.

"Early-stage prostate cancer can typically be treated very well with radiation alone and with a high success rate," Dr. Kuban said.

Surgical options

Surgery comes in even more forms, but all share one goal: removal or destruction of the entire prostate gland.

The standard in radical prostatectomy is the open retropubic approach. In this type of surgery, a small midline incision is made below the navel down to the pubic bone, which allows access to the bladder and prostate. Another method is the perineal approach, entering between the scrotum and the anus. Unfortunately, the perineal



Dr. Kuban (l) and Dr. Pettaway (r) review bone scans with Dr. Christopher Stage (center), a resident in the Department of Urology.

approach does not allow lymph node sampling. But in patients with low-risk disease this is acceptable.

Laparoscopic surgery is increasingly being used for radical prostatectomy. "With laparoscopy, you can sample the lymph nodes and remove the prostate as completely as you would with an open incision, using five smaller incisions," Dr. Pettaway said. "Laparoscopic prostatectomy is a challenging procedure and requires specialized training."

Early data seem to show that there is less blood loss with this procedure than with conventional surgery. It also appears that the laparoscopic procedure allows a quicker recovery. "My feeling in talking to patients is that the ones who undergo laparoscopic prostatectomy may be getting back to normal activity a little bit quicker, maybe a week or two sooner than with the open approach," Dr. Pettaway said.

Cryosurgery is making a resurgence due to technological advances. Previously, it was impossible to be certain the entire prostate gland was being frozen without also destroying surrounding structures. As in the external beam

radiation therapy, the advent of sonography has allowed for much more precise monitoring of the procedure. In addition, the development of a urethral warmer and temperature probe monitors placed near the rectum and external sphincter have helped decrease complications.

The next step into the future of prostate surgery is robotic surgery. "The surgeon actually performs the surgery by sitting at a remote console," Dr. Pettaway said. "The robot is at the bedside with a human assistant." Ports are placed just as in laparoscopic surgery, and the robot's hands manipulate the instruments in response to movements made by the surgeon at the remote console. The biggest benefit is that the surgeon is looking at a three-dimensional image rather than trying to interpret a two-dimensional image, as in laparoscopy. "Most urologists who have tried robotic surgery say they really like it," Dr. Pettaway said.

Nerve grafts, gene therapy, and other advances

One of the biggest concerns among patients being treated for prostate

cancer is maintaining sexual function. Radical prostatectomy can include the severing of one or both cavernous nerves in order to obtain negative surgical margins. This can dramatically diminish erectile function. To address this issue, surgeons recently have begun taking the sural nerve from the leg and grafting it between the two cut ends of the cavernous nerve. Early studies in humans showed that about half the men who had the sural nerve graft were able to have erections, as opposed to about 5% of those who had a bilateral non-nerve-sparing procedure. Researchers are currently trying to determine whether sural nerve grafting would also be beneficial for men who have had only one cavernous nerve severed.

Other researchers are working with radiosensitizers and radioprotectors, drugs that make the tumor more sensitive and the healthy tissues less sensitive to the effects of irradiation. Gene therapy is also the focus of current study in the hope that researchers will find a genetic "off switch" for tumor growth.

With all these advances, when treatment of early-stage prostate cancer is required, it is now quite feasible. But the next step goes beyond treatment.

"We've moved all the way from treating prostate cancers at a relatively advanced stage to finding and treating them at a very early stage in many instances," Dr. Kuban said. "But now we want to back up even further and look at preventing them altogether." For example, M. D. Anderson is leading a large, multicenter trial to investigate whether vitamin E and selenium may be effective in preventing prostate cancer.

And no matter how technologically advanced the treatment, prevention is always a preferable option. "That would actually be the best that we could offer the patient," Dr. Kuban said. ●

FOR MORE INFORMATION, contact Dr. Kuban at (713) 563-2329, Dr. Pettaway at (713) 792-3250, or Dr. Mathew at (713) 792-2830.

Everyday Drugs Show New Promise for Cancer

Several common drugs for arthritis and cardiovascular disease are now being studied for their cancer-fighting abilities. If these drugs prove effective in preventing or treating cancer, many Americans may already have benefited inadvertently.

by Katie Prout Matias

No one thinks much about the wonders of aspirin, that innocuous and bitter tasting little white pill. Did you know, for example, that it journeyed to the moon in 1969, or that it was actually prescribed 2,400 years ago by Hippocrates? He found that chewing on the bark of the willow tree, which contains the natural form of aspirin, relieved aches and fevers. Most impressive is that, in addition to combating arthritis and cardiovascular disease, aspirin may even have the power to prevent certain forms of cancer.

Aspirin may not be the only common drug to have this unexpected and beneficial side effect; several other arthritis drugs, as well as some cholesterol drugs, have also been associated with a reduced incidence of cancer among long-term users in multiple retrospective studies. As part of the ongoing search for less toxic and less expensive cancer therapies, researchers at M. D. Anderson Cancer Center are investigating noncancer pharmaceuticals for their chemoprevention and cancer treatment potential.

Chemoprevention with NSAIDs

The old saying “Take two aspirin and call me in the morning” is now more or less being applied to patients at increased risk for colorectal cancer. Long-term daily aspirin use has been shown to cut colon polyp formation by as much as 35%, so many physicians are now prescribing low-dose aspirin to patients at high risk for colorectal cancer. “There is a huge body of epidemiologic data in support of aspirin, and aspirin is cheap as dirt,” said Patrick Lynch, M.D., J.D.,

an associate professor in the Department of Gastrointestinal Medicine and Nutrition. “The only thing that gives me any reservation about recommending that everyone at increased risk for colorectal cancer take low-dose aspirin is the somewhat unpredictable side effects, gastrointestinal bleeding and ulcers.”

In recent years, scientists have developed so-called “super aspirins,” the cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex). Often used in treating arthritis, the newer non-steroidal anti-inflammatory drugs are just as effective as aspirin at relieving pain but have fewer side effects. Aspirin’s side effects are a result of its nonspecific blocking action against two cyclooxygenase enzymes, COX-1, which is needed for healthy mucosal tissues, and COX-2, which is produced during inflammation and by precancerous tissues. Celecoxib blocks only COX-2, the one implicated in cancer risk. (See “Are COX-2 Inhibitors Safe?” on page 5).

According to Banu Arun, M.D., an assistant professor in the Department of Breast Medical Oncology, who is studying the use of celecoxib in breast cancer prevention, COX-2 inhibitors have antiproliferative, apoptosis-increasing, and antiangiogenic effects.

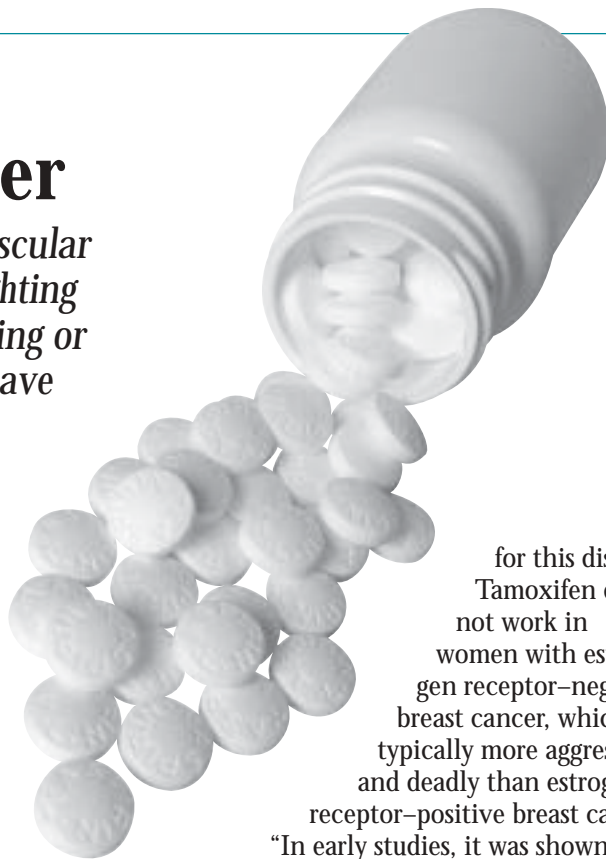
In her study, Dr. Arun wants to determine whether celecoxib might provide protection for women at increased risk of breast cancer who cannot take tamoxifen, the only preventive agent approved

for this disease. Tamoxifen does not work in women with estrogen receptor-negative breast cancer, which is typically more aggressive and deadly than estrogen receptor-positive breast cancer.

“In early studies, it was shown that COX-2 inhibitors prevent both of these types of breast cancer,” said Dr. Arun. “In our current prospective study, the patients are given the drug either for six or 12 months, and then we look at tissue endpoints. We are looking at markers in the breast associated with risk and evaluating the reversal of these markers. If we can show reversal of these markers, then that agent can be taken to the next step.” The markers they are looking at include cellular atypia, proliferation index, p53, HER2/neu, and apoptosis.

Celecoxib has shown potential for use in preventing other types of cancer as well, including bladder, esophageal, skin, brain, lung, and head and neck cancer. The strongest evidence to date is in colorectal cancer prevention: In a study published in the *New England Journal of Medicine* in 2000, Dr. Lynch and others found that celecoxib reduced the number of polyps in patients with familial adenomatous polyposis (FAP), a hereditary disease that leads to the formation of hundreds to thousands of colon polyps and a 100% colorectal cancer rate by age 40 or 50. As a result of that study, the Food and Drug Administration approved celecoxib in 1999 as adjunct therapy for patients with FAP.

More recently, Dr. Lynch completed a phase I study of celecoxib in children



with FAP and plans to begin a large, multicenter, international phase II/III trial this winter. "If we have a drug or drugs that could stabilize polyps and keep them from becoming cancerous or increasing in number and size, it might make them more manageable endoscopically," he said. "We might be able to delay prophylactic removal of

the colon, which is a major surgical procedure."

Revisiting cholesterol-lowering drugs

Considering that an estimated 13 million Americans take statins to lower their cholesterol, recent findings that statins may reduce the risk of several

kinds of cancer could result in these drugs inadvertently lowering the country's overall cancer rates. Recent studies suggest that statins may bring about a 30% lower risk of breast cancer in postmenopausal women, a 58% lower risk of prostate cancer, and a 46% lower risk of colorectal cancer, as well as reduced
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Are COX-2 Inhibitors Safe?

by Dianne Witter

Cyclooxygenase-2 (COX-2) inhibitors have become a staple in the arsenal of non-steroidal anti-inflammatory drugs, considered as effective as aspirin without the gastrointestinal side effects. Recently, the COX-2 inhibitor celecoxib (Celebrex) has shown substantial promise for treatment and chemoprevention of cancer, and is currently the focus of more than 40 National Cancer Institute (NCI) trials around the country, some at M. D. Anderson Cancer Center.

But with the recent voluntary recall of rofecoxib (Vioxx), another COX-2 inhibitor, from the market due to concerns that it may cause increased risk of cardiovascular problems, many physicians—and their patients—are wondering whether all COX-2 inhibitors might pose similar safety problems.

In response to the recall, the NCI is conducting a rapid but thorough review of data from long-term trials of COX-2 inhibitors through its Data Safety Monitoring Boards. However, scientists say that Vioxx and Celebrex differ substantially in their molecular makeup and in how long they stay in the body. They're thought to work through different cellular pathways and therefore may be less likely to cause the same problems.

"COX-2 inhibitors differ in their degree of COX-2 specificity and inhibitory activity and probably

more importantly in their interactions with non-COX-2 targets," said Bernard Levin, vice president for cancer prevention and population sciences at M. D. Anderson and co-principal investigator of a study using celecoxib as a chemoprevention agent for colorectal polyps. "Three long-term international trials of celecoxib are undergoing careful scrutiny to assess whether there is any evidence of cardiovascular harm, and this information should be available within the next few months."

The experience with Vioxx, however, is a valuable reminder that, no matter what the safety record, all drugs have some risks. The decision to prescribe a drug or to study a drug in a clinical trial requires carefully weighing the potential risks and benefits. This is especially important in the field of chemoprevention, in which new agents must be studied for years to determine their preventative effects.

"An agent used over many years by patients who are asymptomatic and may not have a serious disease



Dr. Banu Arun, an assistant professor in the Department of Breast Medical Oncology, is studying the possible role of celecoxib in the prevention of breast cancer. To ensure patient safety, the data from all ongoing, long-term trials of COX-2 inhibitors are undergoing intensive review by the NCI.

has to meet high safety standards," Dr. Levin said. "The best way to determine if a drug has any adverse effects is in long-term, randomized, blinded, placebo-controlled trials monitored by independent Data Safety Monitoring Boards with appropriate expertise." ●

Everyday Drugs Show New Promise for Cancer

(Continued from page 5)



Dr. Khandan Keyomarsi (r), an associate professor in the Department of Experimental Radiation Oncology, has successfully used statins to stop the uncontrolled growth of cancer cells in laboratory studies of several cell lines. Here, she reviews films with **Dr. Ekem Efuet**, a postdoctoral fellow.

pancreatic cancer and melanoma rates in laboratory animals.

While multiple retrospective studies have looked at statins for chemoprevention, one researcher at M. D. Anderson is studying them for cancer therapy. In a study presented at the 2003 Annual Meeting of the American Association for Cancer Research, Khandan Keyomarsi, Ph.D., an associate professor in the Department of Experimental Radiation Oncology, showed that the prodrug form of lovastatin, one of six statins sold in the United States, stopped the uncontrolled growth of cancer cells in the laboratory.

Dr. Keyomarsi has examined statins using breast, ovarian, and colorectal cancer cell lines and found comparable effects. "The pathway that is affected is pretty ubiquitous in all the different cancers," said Dr. Keyomarsi. "We are basically affecting the brakes in the cell cycles, and this would compromise the growth of most cancer cells."

Statins lower cholesterol by shutting down an enzyme called HMG-CoA reductase. The drugs' potential benefit in cancer could be a result of the fact that the prodrug form of the statins

has a different target than HMG-CoA reductase, and that target affects the basic protein degradation machinery, leading to inhibition of cell growth.

Statins' anticancer effects could also be a direct result of their lowering cholesterol. "I think anything that would put that much stress on the body could have deleterious effects, whether it's in the form of cancer or other diseases," noted Dr. Keyomarsi. "But it's also possible the mechanism has nothing to do with lowering cholesterol." Indeed, the findings have been mixed on whether non-statin lipid-lowering drugs have the same anticancer effects as statins.

If physicians were one day to prescribe statins for cancer prevention or therapy, they would have to take into consideration the sometimes severe and even fatal muscle problems that have been associated with these drugs. As with aspirin or celecoxib, patients would likely have to take the drugs indefinitely for chemoprevention.

Randomized, controlled, prospective clinical trials are needed to confirm whether statins can truly prevent or treat cancer. "Because there's enough

anecdotal evidence out there and enough mechanistic evidence to suggest that these agents could and should be used as chemoprevention agents, there should be clinical trials," said Dr. Keyomarsi.

On the horizon

Researchers at M. D. Anderson and the National Cancer Institute are now setting their sights on another non-cancer drug for the possible prevention of cancer: rosiglitazone. Used to treat type II diabetes, rosiglitazone helps the body use insulin more efficiently. Very early preclinical studies have shown that it also appears to slow the growth of tumors and inhibit angiogenesis.

According to Dr. Arun, she and her colleagues are teaming up with Karen Lu, M.D., from the Department of Gynecologic Oncology, to conduct a clinical trial of rosiglitazone in breast and uterine cancer prevention. "Not only for breast but also for some other cell lines, it was found that the drug decreases the proliferation of tumor cells, which in turn is associated with decreased risk of cancer," said Dr. Arun. "We are going to study this drug in patients who have insulin resistance. Insulin resistance has been linked to an increased risk of uterine as well as breast cancer, so these patient populations are actually ideal to study with this drug."

While the idea that relatively non-toxic drugs that so many people are already using could be preventing some kinds of cancer is doubtless exciting, Dr. Lynch urged caution in viewing them as a cure-all. "We don't have any magic bullets," he said. "We have agents that can reduce risk, but the long-term benefits or risks are not known. The need for periodic surveillance has not gone away. The search for newer, better drugs continues."

Take caution, given the recent lessons learned from Vioxx. ●

FOR MORE INFORMATION, contact Dr. Lynch at (713) 794-5073, Dr. Arun at (713) 792-2817, Dr. Keyomarsi at (713) 792-4845, or Dr. Levin at (713) 792-3900.



Myths & Facts about Cancer Prevention

The word “cancer” strikes fear in the hearts of Americans. A lot of misinformation about cancer stokes that fear. Is there really anything we can do to prevent these diseases? Aren’t most cancers inevitable anyway?

Here are some of the myths about preventing cancer—and the latest facts:

MYTH

There is nothing I can do to prevent cancer.

FACT:

Wrong! Up to two-thirds of all cancers may be preventable if you avoid tobacco, eat a healthy diet, exercise regularly, protect yourself from the sun, limit or avoid drinking alcohol, and get recommended screenings regularly.

MYTH

Most cancers are hereditary.

FACT:

It’s estimated that only 5 to 10% of all cancers are truly hereditary. Tests can now determine if a person with a strong family history of breast or colon cancer carries the altered genes that put him or her at high risk for these diseases.

MYTH

What to eat—or not eat—to prevent cancer is too complicated for normal people to keep straight.

FACT:

Following some basic guidelines of healthy eating can help you prevent cancer as well as a host of other health problems. Eat at least five servings of fruits and vegetables a day as well as whole grains. Research has shown that people who eat the most fruits and vegetables have a decreased risk of developing several types of cancer. Have two to three servings of low-fat or nonfat dairy products for calcium

every day. Calcium may protect against colorectal cancer.

Obesity has been associated with increased risk of many types of cancer. Eating a nutritious diet combined with regular physical activity can help you maintain a healthy weight and decrease your risk of cancer. Moderate physical activity is defined as 30 minutes or more five days a week.

MYTH

I’ve smoked for 20 years and the damage has been done. It’s too late to stop smoking.

FACT:

It’s never too late. Smokers who quit before age 50 halve their risk of dying in the next 15 years in comparison with those who continue smoking. Smoking is the single most preventable cause of disease, responsible for 87% of all lung cancer cases and 30% of all cancer deaths. It also places the smoker’s family at risk for lung disease.

MYTH

Drinking alcohol has been shown to decrease the risk of cancer.

FACT:

While some studies have shown that limited alcohol consumption may provide heart benefits, drinking alcohol has been linked to cancers of the colon, breast, and liver. When combined with smoking, alcohol greatly increases the risk of head and neck cancer. If you drink, it’s best to limit alcohol consumption to one drink a day for women and no more than two drinks a day for men.

MYTH

Chewing tobacco and snuff are safe alternatives to cigarettes.

FACT:

There is nothing healthy about snuff and chewing tobacco. They are just as addictive as cigarettes and can cause cancers of the throat and mouth.

MYTH

Using indoor tanning beds does not cause skin cancer.

FACT:

Tanning beds produce the same ultra-violet radiation as the sun. Any tan—no matter how you get it—is a sign of skin damage. To prevent skin cancer, limit your exposure to the sun or tanning salons, use sunscreen of SPF 15 or higher when outside, and cover up with protective clothing and sunglasses.

MYTH


Only people with a high risk of cancer need to get cancer screening.

FACT:

All adults should get regular cancer screening exams because early detection provides the very best chance for successful cancer treatment. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

 **(800) 392-1611, Option 3,** within the United States, or

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December 2004

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DiaLog

Neoadjuvant Trials in Prostate Cancer

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The prostate-specific antigen (PSA) screening era has resulted in a stageshift in the pattern of newly diagnosed prostate cancer such that the most common form of advanced disease is the locally advanced form. As metastasis is the principal cause of mortality, treatment failure with surgery or radiation therapy implies in large part the existence of micrometastatic disease at the very outset of the disease. Neoadjuvant or adjuvant therapy in prostate cancer is directed toward eliminating such sources of treatment failure.

Hormonal therapy is highly effective in inducing regressions in advanced prostate cancer, but invariably clones with hormone-independent biology emerge and proliferate. Systemic chemotherapy is being further studied in both the adjuvant and neoadjuvant settings, particularly with the current appreciation of the survival benefits of docetaxel-containing regimens in advanced hormone-independent disease.

One of the hallmarks of effective neoadjuvant therapy in cancer is the achievement of complete pathologic remission at the time of surgery. This landmark has been associated with markedly improved prognosis in many tumor types, but for reasons that are incompletely understood,

complete pathologic remissions are rarely achieved in prostate cancer with neoadjuvant therapy.

At M. D. Anderson, a neoadjuvant multidisciplinary group directs the clinical and scientific approach to high-risk prostate cancer. An important focus is on understanding the molecular mechanisms of prostate cancer, including those that mediate resistance to hormonal therapy and chemotherapy as well as those that contribute to the early events of metastatic disease. A range of therapeutics, including angiogenesis inhibitors and signal transduction inhibitors (alone and in combination), is being studied, with molecular and pathologic endpoints in mind.

For example, we are completing a trial of hormone ablation, docetaxel, and imatinib followed by radical prostatectomy in men with high-risk localized disease. Imatinib is a tyrosine kinase receptor inhibitor. The kinase is found not only in primary tumors but also in the bone microenvironment where metastatic prostate cancer cells gain a particular advantage. It has also been implicated in hormone-independent signaling pathways. By challenging cancer cells simultaneously with imatinib, hormone therapy, and chemotherapy, we hope to gain an important advantage that will translate into long-term benefit. Residual cancer cells at the time of surgery will be profiled using genomic and tissue-based platforms to provide insights into resistance pathways. Such insights will be influential in defining future directions in the treatment of prostate cancer.

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Published by the Department of Scientific Publications-234,
The University of Texas M. D. Anderson Cancer Center,
1515 Holcombe Boulevard, Houston, Texas 77030,
713-792-3305.

Made possible in part by a gift from the late Mrs. Harry
C. Wiess.



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