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The James Buchanan Brady Urological Institute

UPDATE PROSTATE CANCER

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New Drugs for Prostate Cancer: Chemotherapy Transformed

New drugs, smarter drugs, safer drugs, just plain better drugs. The world of chemotherapy for prostate cancer is experiencing an earthquake, and Hopkins is at the epicenter -with a wealth of clinical trials, many of compounds and drug regimens developed at the Kimmel Cancer Center by Mario Eisenberger, M.D., Michael A. Carducci, M.D., Ted DeWeese, M.D., Roberto Pili, M.D., and Samuel Denmeade, M.D.-aimed at an unprecedented spectrum of men.

Gone are the days of last-ditch efforts- waiting to start conventional chemotherapy until everything else had failed, often when men were too sick to tolerate the drugs' harsh side effects, and the cancer had become too aggressive and widespread. Over the last several years, these oncologists, building on a solid basic science foundation of molecular insights into how prostate cancer works, have transformed the "traditional" chemotherapy mindset. They're attacking the disease earlier, and developing an elite cadre of selective drugs aimed at controlling-if not necessarily curing-prostate cancer, and prolonging life for years. "We're using smart' drugs," says Eisenberger. "They work at very specific molecular steps of cancer cell growth. Some of these drugs interfere with those steps; many of them will not cause a response in a traditional way-that is, the PSA may not always drop immediately; it will just remain stable." Because the drugs work differently, their effects must be measured differently, and the newest clinical trials are designed for long-term follow-up.

"We're taking advantage of the current patterns of prostate cancer patients coming to the clinic," Eisenberger continues. "We're seeing more men with early disease, and we believe these are the men who are most likely to benefit from our new compounds. Say a man has a probable lifetime survival, without further treatment, of eight to 10 years. If we could double this time, that man may never die of prostate cancer. So we may not be able to cure the disease, but we may be able to stabilize it-delay the progression in a big way. Because these smart compounds either don't have side effects, or have far fewer side effects than conventional chemotherapy and hormone therapy, they're perfect for men with early disease, and we'll have achieved a benefit that is comparable to a cure."

Clinical trials are available for patients at every stage of prostate cancer. The ever-evolving range of clinical trials is so big that we can only hit a few highlights here. You can find out more about these and other trials by calling (410) 955-8964, or on our website at *http://urology.jhu.edu/research/trials.php* (http://urology.jhu.edu/research/trials.php)

For men with locally confined cancer awaiting radical prostatectomy: Most men have a "limbo" period between the time their cancer is diagnosed by biopsy, and the time surgery is scheduled. Although it can seem like an interminable stretch of time, in the world of clinical trials, it's actually quite brief. Could taking a drug or dietary supplement for a few weeks make a difference in the prostate, on the cancer cells and their rate of growth, and on the growth of nearby blood vessels? Two trials aim to find out. One of them involves the anti-inflammatory drug celecoxib. The other will study the effects of the antioxidant vitamin E and a drug called Sulindac, alone and in combination. For men after radical prostatectomy, whose cancer is likely to recur: These are men who have no evidence of disease, but a risk (based on Gleason score and pathological stage) that the prostate cancer may come back. In one multicenter study, led by Hopkins, men receive adjuvant chemotherapy with docetaxel (Taxotere) -a drug in the taxol family, used for women with breast cancer. Treatment, given weekly, starts at two months after surgery, three out of every four weeks for six months. In prostate cancer, some cells are driven by male hormones, and some are impervious to them. (This is why hormonal therapy is very effective at killing some prostate cancer cells, but it can't kill all of them.) "The idea is that the docetaxel would potentially kill both the hormone-independent and the hormone-dependent cells." There are a few mild, reversible side effects, including fatigue, a risk of a lowered blood count, a risk of tingling or numbness, some swelling in the legs and ankles, and modest hair loss. "This is an aggressive treatment," says Eisenberger. "We're trying to see whether we can prolong the time to PSA relapse," a point when the blood's PSA level starts to climb. "Our objective is to double that time."

get a remission." Building on this study, the Hopkins oncologists are launching new studies to test docetaxel in combination with other drugs, including exisulind, which is related to the antiinflammatory drug sulindac.

For men with a rising PSA after surgery or radiation: One trial for these men features the drug Gleevec. Although the trial is currently full, if early results are successful, "we will build on it," Eisenberger promises. "Gleevec is a smart drug. It blocks the signal for overproduction of a growth factor called PDGF. About 60 percent of the patients in our prior trials appear to overproduce PDGF." In laboratory studies, Eisenberger and colleagues have found that Gleevec appears to stunt the growth of prostate cancer. The drug is already approved by the Food and Drug Administration for use in a form of leukemia, and in a rare intestinal tumor. "With these two diseases, the majority of patients can enter a very remarkable, very impressive remission," Eisenberger says. In another trial, he is also studying Gleevec's effectiveness in men with a rising PSA who are taking hormonal therapy.

Another trial for men with a rising PSA, who have not begun hormonal therapy, features the drug atrasentan, which was developed at Hopkins several years ago by urologist Joel Nelson and Carducci. It blocks a chemical called endothelin, made by the endothelial cells that line blood vessels. Endothelin is linked to both the excruciating, debilitating pain that comes when cancer invades the bone, and the unique bone damage found in some men with prostate cancer, in which the bone becomes unnaturally thick and rock-hard. But it also may have something to do with the progression of prostate cancer-and blocking it, in addition to preventing or easing bone pain and damage, may also slow or halt progression of the disease.

In this trial, led by Carducci, men with a PSA of 0.6 to 5 are given either atrasentan or a placebo. "The goal is to see whether atrasentan delays the progression of PSA's rise," Eisenberger explains. Carducci's research, conducted on men with more advanced cancer, suggests that it can. "In studies of men with metastatic bone disease, without symptoms, who had a rising PSA after hormonal therapy, we found that the men who were treated with atrasentan had a significant delay in the time to progression. What we also showed fairly dramatically, was that the drug seemed to target bone tissue and be protective against damage and pain, while the men in the placebo group continued to progress." That work has led to an expanded Phase III study, under way in the U.S. and Europe.

There are many more drugs being studied, including one that has no name yet- for men with advanced cancer. This drug, called MLN-2704, is genetically engineered to target cells that make PMSA (prostate-membrane specific antigen, an enzyme that's made on the surface of prostate cells). "A monoclonal antibody is hooked up to a chemotherapeutic agent that kills cells," explains Eisenberger, "so it's a smart bomb."

Email: webmaster@urology.jhu.edu (mailto:webmaster@urology.jhu.edu) | 600 North Wolfe Street, Baltimore, Maryland 21287