CHEMOTHERAPY---A NEW FRONTIER
by Diane Cousineau
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Following a diagnosis of prostate cancer, the staging of the disease is every bit as urgent as the finding of it. As we have previously reported on this website: Gleason 7: A New Risk Category, when the pathologist finds that the biopsied tissues are in the Gleason 7 or higher category, the risk that the disease has spread beyond the prostate increases exponentially. Given that, the treatment options might be significantly different than for someone with less advanced disease. There are some physicians who would recommend as primary therapy what is usually considered a second or third phase, more aggressive treatment: chemotherapy, either by itself or in combination.

To pursue this subject, I spoke this month with *Dr. David Agus. Dr. Agus is the Research Director of the Louis Warschaw Prostate Cancer Center (*www.csmc.edu/927.html*) and attending physician in the Medical Oncology Division at Cedars-Sinai Medical Center in Los Angeles and an Assistant Professor of Medicine at UCLA. Before coming to Cedars-Sinai, Dr. Agus was the head of the Laboratory of Tumor Biology at Memorial Sloan-Kettering Cancer Center in New York. His team at Cedars-Sinai is focusing on the factors that affect the development, biology, and progression of prostate cancer, using gene chips and proteomics to understand the on and off switches of the cancer. He also leads the clinical trials programs at the Center, with a goal of facilitating the delivery of new drugs from the lab to the patient.*

DC: Dr. Agus, we have previously reported that a prostate cancer diagnosis with a Gleason score of 7 or higher strongly suggests that systemic (not localized) disease is present. What is your opinion on this?

DA: To determine a Gleason score, biopsied cells are analyzed for differentiation [Note: Differentiation is how different the malignant cells are from normal cells. Low to moderate differentiation signifies a low to moderate grade cancer.] *Gleason 7+ cells are more aggressively malignant and therefore have the ability to survive outside of the prostate. But I think we should approach this question in a different way: Even if a man's prostate cancer could be cured the day before his prostatectomy, there are still prostate cancer cells circulating. So the key question is: Are genes turned on in his system that would allow prostate cancer cells to survive outside of the prostate?*
There are some complicating factors here also. Not all biopsies are equal--they vary widely in detail and breadth depending on the experience and credentials of the pathologist. And, of course, every patient is unique. This is still an art, not a science. What is needed is a technology that will help us sub-categorize biopsies for a more precise and individual diagnosis. The tools that will let us do that, proteomics and genomics, are still in the testing phase. We just have Gleason scores and PSA's to guide us now.

DC: Beyond the DRE and PSA, what other tests do you use and what other factors do you consider before determining which treatment to prescribe to your patients?

DA: I would order a bone scan and CT scan of the chest, abdomen, and pelvis to use as a baseline and to see if the cancer has progressed into those areas. If there were a high Gleason score, a high tumor volume in biopsy, and/or a negative DRE, I would also recommend an endo-rectal MRI, again looking for local progression. If the man has first degree (father, brother) or multiple second degree (uncle, cousin) relatives who have or had prostate cancer, I would begin testing earlier (beginning at age 35) and test more often. Without family history, I would begin PSA and DRE testing at age 40.

DC: So given a scenario with the strong possibility that the cancer has spread beyond the prostate, is it best to attack the cancer with more than the traditional approach of hormones and/or radiation? Are there any cases where you would go directly to chemotherapy as a first-line treatment? Would you ever interrupt a current course of treatment or combine it with chemotherapy?

DA: The short answer is, "I don't know." Treatment decisions today are data driven and value-based, not numerical. While there are several excellent nomograms that help predict outcome, there is no specific percentage chance of relapse above which a patient should have more aggressive therapy. Treatment decisions are made by the patient together with his physician and family. I would take it case by case, of course, and normally wait until the current course of treatment is finished to see if it worked. If the current treatment was not successful, I would probably recommend chemotherapy to reduce the size of the gland and follow it up with radiation. I would most likely recommend a clinical trial for neo-adjuvant therapy [a chemotherapy or molecular treatment before traditional therapy]*. This will hopefully (although not proven) increase the chance of a cure by reducing the size of the gland and therefore the amount of cancer so it can be targeted more effectively. This type of therapy is the subject of clinical trials at our Center and others across the country. My role is to empower and educate the patient about a manageable number of options so they can make a treatment decision. I would say, for example, "What if I can help you live six more months and here are the side effects you can expect to encounter." On the other hand, if there is no benefit to undergoing further treatment, I will tell him that too. These are very individual decisions that should always consider their quality of life as well.*

DC: Before we discuss the chemotherapy regimen in detail, let me digress a minute to ask you a question about hormones. Urologists use hormonal therapy after primary therapy has failed and the patient is likely to be hormone refractory. It seems counter-intuitive to then treat them with hormones.

DA: I think it's more a matter of semantics. Their condition is not truly 'hormone refractory'. An absence of hormones doesn't slow the growth of the cancer in this setting. The androgen pathway is still active even though the hormones have been controlled at a low level. Charles L. Sawyers at UCLA has done an excellent study [www.research.ucla.edu/chal/99/dday/article04.htm*] showing that, over time, the testosterone receptors are active in the relative absence of androgen. His team is continuing to define the molecular wiring in prostate cancer tumors and search for drugs that will target this pathway.*

DC: What kind of chemotherapeutic agents do you use? Are there any new drugs on the horizon?

DA: The gold standard is taxotere given every three weeks, which has been proven to lengthen life. There are many others in trial, but they are experimental and there is too little data to use outside of a clinical trial. The good news is that there were just a few drugs available a few years ago and now there are many. In addition, another group of drugs, epothilones, shows great promise. [Note: Epithilones are similar to taxanes (Taxol, Taxotere), but are more active and effective, even in cases where common chemotherapy has failed.] *Epithilones are in Phase 3 testing now. Remember the drug approval system still works backwards---drugs are developed for advanced cancers and then, once they are proven efficacious, rolled back to less advanced cases.*

DC: Please tell us more about the chemotherapy process: is high dose better than low dose over a longer period of time; how do you measure how well it is working; does it slow down or stop the cancer?

DA: How the patient feels is the best indicator of how well it is working. I always have to assess: are their symptoms better? Plus I continue to monitor their PSA and get regular CT and bone scans. That is very important. As for dosage levels, there is little data showing that high dose is better than low dose. In the case of the taxotere and prednisone combination that the FDA approved for advanced prostate cancer patients, they found that giving a higher dose every three weeks was better than a low dose every week. But the appropriate levels are very individual. For example, many prostate cancer patients are elderly, so it can be harder for them to tolerate certain regimens. They can still benefit from therapy, but their toxicity levels must be monitored carefully. Any therapy has side effects, and chemotherapy definitely has significant side effects. These need to be discussed with an individual's physician to determine the "risk" for that patient. We can look forward to the molecular-directed drugs that are being tested now because they will have far fewer side effects.

I think the lack of progression of the cancer is more significant than eliminating it completely. We will never cure advanced disease. It's my opinion that some drugs with good potential have been thrown out because they only showed a 50% reduction in the cancer. What if the cancer growth was stopped? I think we should change our goal to making prostate cancer a chronic disease by slowing its progression. We should be doing as little as possible for as long as possible.

DC: What can you tell us about the next generation of chemotherapy and drugs for the treatment of prostate cancer?

DA: As I mentioned before, there are dozens of drugs and treatments being tested. It's good news that the FDA has approved drugs for use with advanced prostate cancer because it will stimulate more researchers and drug companies to proceed with similar trials. Supportive care medications that target bone, for example, are also very important. Zoledronic acid (Zometa) has had a marked impact on the treatment of prostate cancer patients with bone metastases.

The medical community together with the biotechnology and pharmaceutical industries are on the cusp of developing drug regimens that are designed for each individual and their specific cancer. Soon, we will be able to use a blood sample to visualize all the proteins at once and produce a complete protein (proteomic) profile of that patient. In the past, we used biopsied tissues in paraffin blocks. Every time we wanted to re-test, we had to re-biopsy. Using serum proteomics, we only need a drop of blood. The profile of one patient generates about 40 gigabytes of data and we now have the computing power that this requires. In the near future, we will use this profile, together with information from other technologies such as genomics to pick the right drug for the right patient. This will develop over the next several years and is just being applied now. For example, there is now a test using genomics that can predict the likelihood of relapse in a breast cancer patient. It's not science fiction anymore.

DC: Thank you so much for your time, Dr. Agus. It must be exciting to be in the forefront of research, especially now. We look forward to seeing what your team is developing.