
Solving the Puzzle

Prostate Forum

Unusual Cases

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Puzzle Points

-  Prostate cancers that reach a large size in the pelvis without spreading to bone and other sites appear to lack proteins needed for metastatic spread.
-  Patients with widespread lymph node involvement, a high PSA, and no bone metastases commonly respond very well to hormonal therapy.
-  Patients who have widespread bone involvement and a PSA under 10 ng/ml respond well to initial hormonal therapy. However, they rapidly develop resistance to standard hormonal therapy and chemotherapy.
-  Neuroendocrine prostate cancer is extremely variable in its response to treatment and in survival. These cancers appear to be driven by cAMP and IGF1. Treatments that target this two factors may have promise as treatment of this form of prostate cancer.
-  Chromogranin A is often elevated by proton pump inhibitors, but there is no evidence that this leads to prostate cancer progression.

Unusual Forms of Prostate Cancer

Prostate cancer is one of the most variable human cancers. This issue of *Prostate Forum* is devoted to a discussion of the unusual forms of prostate cancer I often find in my practice or read about in the medical literature. The standard prostate cancer is an adenocarcinoma that spreads in a predictable fashion from the prostate gland to the lymph nodes in the pelvis, and eventually to bone. Additionally, standard prostate cancer makes a series of proteins, such as prostate specific antigen, prostatic acid phosphatase, and prostate specific membrane antigen. As I have discussed in earlier issues of this newsletter, large variations occur in the speed at which different cancers grow and spread (even with standard prostate cancer). I've also discussed how Gleason grade, PSA doubling time and other tools help us anticipate how dangerous a man's cancer is and how aggressive his treatment needs to be. However, any clinic that sees a large number of prostate cancer patients will encounter cases that deviate from the well-established behavior of the common adenocarcinoma of the prostate gland.

Extensive Hormone Refractory Cancer In the Pelvis Without Distant Metastatic Disease

There is a distinct subset of men who present with prostate cancer that is initially limited to the pelvis and that remains limited to this site despite aggressive use of hormonal therapy. Even when these cancers become hormone-refractory, they remain limited to the pelvis. While chemotherapy may initially prove effective, these cancers eventually become refractory to available drugs. At some point along the way, the cancer in the pelvis enlarges to the point that it blocks the flow of urine out of the bladder or blocks the rectum or adjacent sigmoid colon. Many of these patients require diversion of either the ureters or colon to the skin because of this blockade. Because these cancers do not readily spread to bone, the cancer can become quite extensive without threatening life.

In 2004, Dr. Logothetis and his colleagues at MD Anderson did a superb job characterizing a series of these cases. In addition to describing the clinical details of this form of prostate cancer, they examined the molecular changes that might account for this unusual behavior. These cancers did not express certain proteins characteristic of aggressive metastatic disease. The cancers that are locally extensive without metastases do not make these metalloproteinases. For example, matrix metalloproteinases are proteins that allow the cancer to digest through tissue barriers to metastatic spread. As I will discuss later in this newsletter, prostate cancer cells can make proteins normally found in nerve tissue that are called neuroendocrine markers and this tends to correlate with the early development of metastatic disease and hormone-resistance. These localized cancers did not make any neuroendocrine markers.

In normal prostate epithelia cells, the cells line the prostate gland and ducts. These cells are stuck together by two molecules that act like Velcro, causing adjacent cells to adhere to one another: E-cadherin and beta-catenin. These cancers produced

a lot of both components of this Velcro-like material and that may explain why these cancers have such a difficult time spreading to bone and other sites; the cancer cells are glued together and therefore cannot escape into the blood stream.

You may well ask what is the best way to manage these types of cancers? Well, I think the ideal approach would be to eliminate them before they can cause problems. These cases illustrate the benefit of performing a radical prostatectomy or doing radiation therapy before the cancer becomes too extensive. In the MD Anderson paper, the patients were subjected to salvage prostatectomy. In general, I have also favored salvage prostatectomy in cases like this. Much to my surprise, though, I have also had a few patients do quite well with robotic prostatectomy. In one recent case, a patient with a 150-gram cancer had the mass successfully removed with only modest postoperative problems. Other options may be in the wings. With the development of highly focused radiation therapy such as Trilog, Tomotherapy, or Cyberknife, radiation therapists can also do a much better job in treating large prostate cancer within the pelvis. In practice, I try to find a drug or hormonal treatment program able to reduce the cancer to the smallest extent possible before sending the patient for surgery or radiation therapy.

There is one area of research that may end up providing an elegant solution to this problem by harnessing the immune system to attack the cancer mass. Drs. Ragde and Bahn have been testing direct injection of dendritic cells into prostate cancer masses and the early results look promising. Certainly, if successful, this approach would be much less traumatic to the patient than either salvage surgery or radiation therapy. This new development is interesting because Dr. Ragde is widely regarded as the father of modern seed implantation and has a long history of being an important innovator in prostate cancer treatment.

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Advanced Prostate Cancer With Only Lymph Node Involvement

As I have discussed in the last few issues of the newsletter, prostate cancer usually spreads from the prostate gland to the lymph nodes in the pelvis and then to bone. However, there are occasionally men who present with prostate cancer that has spread to the lymph nodes outside of the pelvis yet do not show any evidence of bone involvement. These men often have very high PSA levels. Below, I have listed those papers I can find on this subject. One interesting point made by several of these authors is that the men did unexpectedly well with hormonal therapy with excellent initial responses and without the expected development of hormone-resistance. During my career, I have seen a number of such cases, the first of which was my first prostate cancer patient. This man was a homicide detective from New Orleans who had been one of the patients initially treated by Ferdinand Labrie in his "complete androgen" blockade trials. He had eventually progressed through that treatment and entered our clinical trial testing suramin as a treatment for prostate cancer. He proceeded to have a very dramatic response to suramin. In fact, his was the best response we had to that drug while I was at NCI.

Another patient I'd treated had been diagnosed years earlier at Massachusetts General Hospital with a PSA in excess of 3,000 ng/ml and widespread involvement of lymph nodes throughout his body. While he did not have bone metastases, he was in kidney failure because the lymph nodes were blocking the flow of urine down the ureters. He went on to have a spectacular response to hormonal therapy with normalization of his kidney function. Now, years after his diagnosis, he still is not hormone-resistant and does not have bone metastases.

The third patient arrived at my clinic, AIDP, in the fall of 2005. He had an initial PSA of 3,600

ng/ml. At that time, he had extensive pelvic and retroperitoneal lymph node involvement, but no bone metastases. We started him on an LHRH agonist, Casodex, and Avodart. After 6 months of therapy, his PSA was less than 0.01 ng/ml, but the CT scan still showed enlargement of his retroperitoneal lymph nodes. By 10 months, even the CT scan showed no evidence of disease. After one year he was taken off hormonal therapy. As his testosterone recovered, his PSA increased from less than 0.01 ng/ml to 0.1 - 0.2 ng/ml and has been stable in this range ever since. His last PSA, done 18 months after the end of hormonal therapy, remained stable and bone scan and CT scan showed no evidence of metastatic cancer. Ultrasound exam still showed cancer present within the prostate gland.

In summary, these cases are not only characterized by limited spread to the lymph nodes, but also by an inability to spread to bone and to develop hormone resistant disease. Only one paper has attempted to understand why these cancers seem so limited in their spread. A group of hormones called chemokines are known to determine where cancer cells spread. Heresi, et al. looked at the chemokine receptor expression in one case of generalized nodal involvement. They found abundant expression of chemokine receptor CCR7 in one case of extensive nodal involvement. Interestingly, CCR7 has been reported to be involved in the spread of breast, lung, and uterine cancers as well as melanoma. Because of its involvement in other, common cancers, we may soon have a better understanding of the role CCR7 has in these unusual cases.

Clinically, these patients are recognized by three criteria: widespread lymph node involvement, the absence of bone metastases, and a very high PSA. To make things a bit interesting, lymphomas typically present with widespread lymph node involvement. One case of Hodgkin's lymphoma has even been reported to produce high PSA levels! So, even if the PSA is high, the diagnosis needs to be confirmed by a biopsy.

The key point you should take away from this article is that widespread metastatic disease and a

high PSA do not always mean that hormonal therapy will prove of little value. If you have this particular pattern of metastatic spread, you may actually do very well on hormonal therapy.

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Extensive Metastatic Disease With A PSA Less Than 10 ng/ml

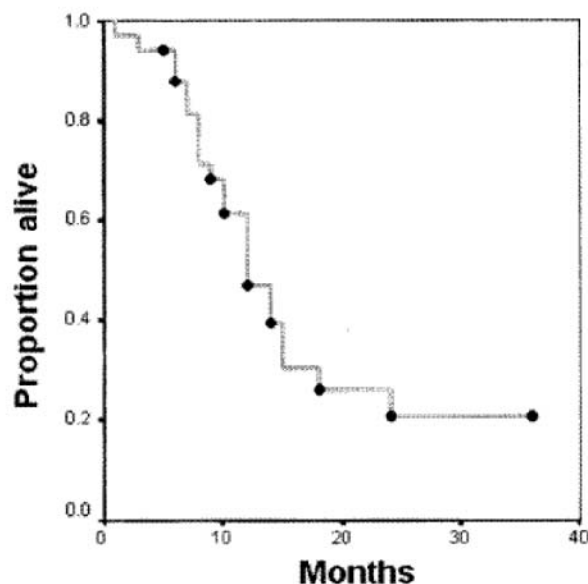
Every so often, I encounter patients with a relatively low PSA and extensive metastatic disease. Biologically, these cases are the opposite of the patients I have just discussed. While men like this typically respond well to initial hormonal therapy, they develop hormone resistance quite rapidly. Similarly, responses to current chemotherapy are often not very durable. While these patients start out with a low PSA, by the time they become hormone resistant they commonly produce no PSA at all.

But how common is this form of prostate cancer? In one study on the value of bone scans in newly diagnosed patients, out of 861 patients with a PSA less than 20 ng/ml, only 8 had a positive bone scan. This means that these patients are a bit less than 1% of all newly diagnosed cases. I think this is roughly correct.

Figure 1 (on the next page) shows the survival of these patients when treated by standard hormonal therapy and chemotherapy.

As you can see, approximately 80% of the patients have died two years after diagnosis. There is general recognition that these patients do not benefit from standard treatment options and this is an area where research is ongoing. If you find yourself with this form of prostate cancer, it really makes sense to contact a center specializing in prostate cancer to see if they have a special program or clinical trial designed with this disease in mind. One promising approach is to start chemotherapy before hormonal therapy or administer it with the hormonal therapy. At AIDP, we have

Figure 1



had some success with the rapid move from initial hormonal therapy to second line hormonal therapy with radiation therapy to any actively growing metastatic sites. Only time will tell which of the current approaches will prove successful.

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Neuroendocrine Carcinoma Of The Prostate Gland

Neuroendocrine cells are found in the normal prostate gland, where they have been shown to produce a range of hormones including serotonin, bombesin, and calcitonin. However, we do not know the role these neuroendocrine cells play in normal prostate biology. In the standard adenocarcinoma of the prostate gland, neuroendocrine cells

are nearly always found scattered throughout the cancer mass. In this setting, these neuroendocrine cells do not make PSA, are not growing and do not have the androgen receptor. In the test tube, even though the neuroendocrine cells do not grow, the hormones produced by these cells are capable of fueling the growth of the adenocarcinoma cells. One report claimed that in the prostate cancer specimens obtained at surgery, the prostate cancer cells near the neuroendocrine cells were growing more rapidly than those distant from these cells. This suggests that the neuroendocrine cells might fuel prostate cancer progression. In fact, the larger the proportion of the cancer mass composed of neuroendocrine cells at diagnosis, the more likely the patient would do poorly over time.

While serum chromogranin A has generally been found to be the best marker to detect the development of neuroendocrine cells in prostate cancer, there is some evidence that it is more than just a marker. For example, if you add chromogranin A to prostate cancer in tissue culture, it triggers the formation of proteins that improve the cancer cell's resistance to treatment.

In prostate cancer research, there are certain classic studies that define issues with great clarity. In 1991, Kadmon, et al. showed that an elevated chromogranin A level made evolution of hormone resistance more likely. Furthermore, once hormonal therapy started, chromogranin A levels initially increased in many patients, but would later decline back to normal. When chromogranin A levels stayed elevated or when it started to increase late in hormonal therapy, hormone resistance was very likely to follow. This observation has been repeatedly confirmed.

Up to this point, we have been discussing the impact of neuroendocrine cells that are not themselves capable of growth and where the impact appears to be thought an effect on the prostatic adenocarcinoma cells. In small cell carcinoma of the prostate gland we have neuroendocrine cells that are able to rapidly grow and spread. Again, these cells make very little or no PSA and make little or no androgen receptor. While they can make chro-

mogranin A and other neuroendocrine markers, in many cases they make no detectable markers. Chris Logothetis has published the best clinical characterization of this form of prostate cancer in a Phase II clinical trial in which he and his colleagues tested a chemotherapy combination containing doxorubicin, etoposide, and cisplatin. They observed that this form of prostate cancer differed from the common form of prostate cancer in that: PSA levels were frequently low and bone metastases were usually bone destructive rather than dense. Also, small cell prostate cancer commonly spreads to liver and lung. Responses to chemotherapy were short and median survival was 10.5 months. Interestingly, measuring neuroendocrine markers like chromogranin A did not provide any useful information about likely survival.

Susan Slovin has recently written what I think is the best overview of the diagnosis and treatment for all forms of neuroendocrine prostate cancer. One of the most useful points she makes is that the actual behavior of neuroendocrine prostate cancer is extremely variable. While it typically responds poorly to hormonal therapy and chemotherapy and is rapidly lethal, some patients appear to respond well to treatment and have a long survival. The point is that patients should not give up hope, but rather proceed through treatment because there is some chance they might respond well and benefit. This certainly fits what I have seen in my clinic where some patients have done very well.

Before I discuss new treatment options for these patients, I should first discuss what causes the formation of neuroendocrine cells. I'll then base my discussion on the mechanisms involved.

The first real hint about the genesis of these cells came in a paper by Jane Trepel and her colleagues in 1994 at the National Cancer Institute. This group showed that a chemical called cyclic AMP (cAMP) would cause prostatic adenocarcinoma cells to convert to neuroendocrine cells. cAMP is formed inside cells in response to a range of hormones and growth factors. Subsequent studies have shown that hormones and cytokines that induce cAMP do cause the same switch from adenocarci-

noma to neuroendocrine cells. Furthermore, this switch is reversible. The next step was to determine how cAMP caused this switch. My neighbors at University of Virginia, Drs. Parsons and Cox, provided the answer. Protein kinase A is a well-known target of cAMP action, as cAMP activates this kinase. Parsons and Cox transferred a form of protein kinase A that is active even without cAMP into prostate cancer cells and the prostate cancer cells become neuroendocrine cells. They have since shown that mixing these neuroendocrine cells with prostate adenocarcinoma cells accelerates growth of the cancer, especially following androgen withdrawal. Since protein kinase A has well-studied effects on cancer cell biology, much of the rest of the basic science story is now clear.

There is a second pathway that must be engaged for neuroendocrine prostate cells to perform. Growth hormone is key to growth: a lack of it can cause dwarfing and excess can cause people to become unusually tall. Growth hormone does not usually act directly. Instead, it causes the liver to produce insulin-like growth hormone-1 or IGF1, which is then responsible for many of the effects of growth hormone on the body. IGF1 works by binding to a receptor on the surface of the cell and this triggers the activity of a pathway of proteins inside the cell that control growth. A large and growing body of evidence links IGF1 to the development and progression of prostate cancer. In particular, IGF1 and the proteins inside a cell linked to this hormone appear critical to the development of hormone-resistant prostate cancer. It turns out that the IGF1 pathway must be activated within the cancer cell for cAMP and protein kinase A to cause the conversion of prostate cancer cells to neuroendocrine cells. It is because the IGF1 pathway is important to a wide range of cancers that there is an extensive research effort in progress to find the ideal drug to block this pathway.

Knowing what we do about how neuroendocrine cells form, it would seem logical to attack these cells by blocking the IGF1 and/ or cAMP pathways. The promise of this approach is that it may well allow us to force the neuroendocrine cells

back to prostate adenocarcinoma and then use standard prostate cancer treatments. In fact, efforts in this direction have already been tried. Somatostatin is a naturally occurring hormone that blocks the production of growth hormone. Sandostatin is a drug that mimics somatostatin and that is widely used to shut down the production of growth hormone and thus reduce the production of IGF1. Sandostatin has been used to treat hormone-refractory prostate cancer, but it also has been reported to suppress production of chromogranin A, which it does quite well. In my experience, no matter how elevated the chromogranin A, it invariably returns to normal within one month after the first Sandostatin injection. These results are just what you would have predicted based on what we know about how Sandostatin works and is consistent with prompt reversal of the neuroendocrine transformation of prostate adenocarcinoma. One major problem is that we do not have convincing biopsy confirmation that this has actually happened and until that is provided, it may well be that Sandostatin just shuts down the production and release of chromogranin. Even that would not be so bad as chromogranin itself has been shown to improve the survival of prostate cancer cells to treatment in tissue culture.

Other drugs that target the IGF1 pathway are being developed and tested. Celebrex has been reported to slow prostate cancer progression by blocking Akt, an early step in this pathway. Rapamycin blocks mTOR, a rather late step in this pathway: it and similar drugs are undergoing testing against prostate and other cancers. One possible strategy might be to combine drugs that block at different points along this pathway, such as Sandostatin with Celebrex.

It is relatively easy to outline a treatment strategy for neuroendocrine prostate cancers. However, the actual design and conduct of clinical trials in this area is quite difficult. Earlier I mentioned the review of this field written by Dr. Slavin. One really excellent aspect of Slavin's review is that she clearly describes the variability of the clinical course of these patients. This variability makes it

hard to design good clinical trials or even evaluate the results of existing clinical trials. Regardless of treatment, some patients will do well and others poorly. But did the treatment make a difference? The classic solution to this issue would be to separate patients into distinct groups according to prognosis. It is relatively easy to separate out those with small cell carcinoma of the prostate versus those with adenocarcinoma of the prostate with large numbers of neuroendocrine cells. However, very few institutions will see enough small cell carcinoma of the prostate to do meaningful clinical investigation. Among the patients with large numbers of neuroendocrine cells and an elevated chromogranin A, the clinical course is so variable that it is hard to predict how they will do.

At this point, I would like to bring up some additional complications that you need to know about. Processes other than prostate cancer can elevate serum chromogranin A. Lung cancer can also elevate serum chromogranin levels and neuroendocrine cancers can arise in other organs as well. Then, we have the problem that certain drugs can cause dramatic elevation of chromogranin A. In my clinic, the proton pump inhibitors (Nexium, Acephep, Prilosec) used to treat gastroesophageal reflux are the most frequent offenders. These drugs have the capacity to increase serum chromogranin A in patients who do not have prostate cancer, so the elevation seen in prostate cancer patients cannot be assumed to come from the cancer. Serum chromogranin A levels typically fall rapidly once the proton pump inhibitors are stopped.

One patient who nicely exhibits the proton pump inhibitor phenomenon had a Gleason 4+3=7 treated with radical prostatectomy followed by adjuvant radiation between February and March of 2003. By July of 2004, he started on triple hormonal blockade and remained on this until July 2005. At that point, hormonal therapy was stopped and he was placed on Avodart to block or delay recurrence of his cancer. During the summer of 2006 the patient was on a proton pump inhibitor when information became available about its

impact on chromogranin A. For this reason, we measured his serum chromogranin A level and it was 12 times normal. The patient stopped the proton pump inhibitor and chromogranin A level returned to normal, but has subsequently shown a small rise above normal. This patient has now been off hormonal therapy for almost three years with a PSA under one and no evidence of recurrent disease. This case illustrates the fact that proton pump-induced chromogranin A does not appear to speed prostate cancer progression. However, it is true that it is difficult to identify when the patient's prostate cancer is producing chromogranin A.

What should you do if you have a prostate cancer with neuroendocrine features? These are not common cancers and the appropriate treatment has not been defined. One option would be to get a second opinion from either Memorial Sloan Kettering or MD Anderson, as both have published rather extensively on the clinical management of this disease. At the American Institute for Diseases of the Prostate (AIDP), I am interested in treating neuroendocrine prostate cancer without using chemotherapy. Instead, my major effort is to expand on the observation that Sandostatin may cause neuroendocrine cells to revert to prostate adenocarcinoma. Laboratory results offer the possibility that a Sandostatin-based treatment may well restore hormone-sensitivity to this form of prostate cancer.

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