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“Advanced Prostate Cancer”

Advanced prostate cancer is defined as a disease that is not curable by conventional localized treatments such as radical (open or robotic) radical prostatectomy or radiation. Disease may extend beyond the prostate as determined by the urologist’s digital rectal exam or by different staging modalities including MR and CT; or may be metastatic, that is, known to have spread to other organ systems, often lymph nodes and bones--and perhaps to yet other organs. These types of cancers are often associated with abnormally high Gleason scores on the biopsy/pathology report. Disease may reoccur, as can be true with most other cancers, after what seemed to be curative therapy. The relapse may sometimes show itself only as a rising PSA; or findings suggesting metastases on bone scan or other radiographic studies. Advanced or metastatic prostate cancer may or may not cause symptoms including in the urinary tract, in the pelvis, blockage of kidney(s) urinary drainage or distant pains (such as in the back and other bones) and generalized “not feeling well” and eventually weight loss, poor appetite and difficulty performing everyday tasks of life—also known as “constitutional symptoms”.

If it can be shown that the recurrence is likely in the pelvis (or in the prostate, if it was irradiated but not removed), sometimes another attempt at “local cure” can be offered. This would be radiation after surgical failure or more rarely, prostate removal after radiation failure (latter a far less successful strategy).

What I would like to focus on are patients who have advanced disease despite the above considerations, who have also failed so-called “hormonal therapy”. The latter has been around for over half a century and was initially in the form of castration (removal of both testes) since most prostate cancers are androgen (hormones like testosterone) sensitive--just as the majority of female breast

cancers are sensitive to estrogens. So depriving a prostate cancer of male hormones will get a good response in over 80% of cases. Nowadays, drugs are often used to take the place of either castration or another old-time therapy for prostate cancer, that is, the administration of female hormones. Lupron and other similar long-acting drugs (e.g. Zoladex, Firmaggon, etc.) act through organs at the base of the brain, the hypothalamus and pituitary, to interrupt signaling to the testes to produce testosterone, this achieving a chemical castration. Decreasing testosterone starves and kills off prostate cancer cells. In some cases where it is felt weaker male hormones produced in organs other than the testes (e.g., adrenal glands) need blockade, drugs such as Casodex can be added—these pharmaceuticals act by binding to androgen receptors within the prostate cancer cells.

Men do not die of prostate cancer even with advanced disease, if the cancer is still “hormonally responsive”. Their cancers take a definite turn for the worse when they develop resistance to the basic hormonal control, so-called “hormone-refractory prostate cancer” (HRPC). A rising PSA despite use of e.g., Lupron alone or a combination Lupron-Casodex is a definite harbinger of problems to come. When this occurs, metastases can occur in over a third of patients, even silently, within a few years—even in men who have no symptoms. Some urologists or oncologists will use “secondary” hormonal therapy including cessation of Casodex (if the man is taking this) or use of other steroid drugs such as ketoconazole combined with prednisone.

Further progression of prostate cancer has often been treated with chemotherapy, with the favored current drug being taxotere. As a solo agent, taxotere is more effective than other drugs used in the past, but like many such agents, they can sometimes be poorly tolerated by older men who are frail and have very symptomatic disease such as bone metastases. Taxotere can certainly cause a partial remission (lessening of measurable disease) and can palliate symptoms—but does not cure such unfortunate men. Prolongation of survival versus “placebo” can be measured in months as opposed to years.

There is interest in using taxotere and perhaps newer more specific prostate cancer drugs, recently developed, at an earlier stage of the disease to try to prevent widespread metastases. The more aggressive approach of combining chemotherapy (or “targeted therapy”) with hormonal therapy and either surgery or radiation may have a role in high risk men who have bad (but possibly just localized) prostate cancers at the very get-go. Studies of such multi-modality interventions are not “mature” enough to state there is an advantage versus traditional treatments and “saving the big guns” for relapses.

Newer drugs already available (but expensive!) are targeted at the prostate cancer cells and specifically their hormone (androgen) receptors. As prostate cancer progresses, it genetically may develop more and harder-to-block androgen receptors. Also the so-called Gleason pattern, assigned at the time of prostate biopsy to a newly found cancer, tends to migrate upwards to a higher and more aggressive score if tissue is available for re-biopsy in cases of advanced disease. Zytiga (abiraterone) and “in-the-pipeline” enzalutamide are promising drugs that likely will significantly extend survival even in patients who have progressed after both regular hormonal and chemotherapy.

Provenge is another advance. Although expensive, this therapy is covered by Medicare and many insurance companies and is administered by urologists and medical oncologists. It is a vaccine of sorts made by exposing the prostate cancer patients T-cells (a form of lymphocyte or white blood cell produced in bone marrow and found in blood) to a mixture of chemical substances in a lab--and then reinfusing the “bolstered” cells back into the patient in several office sessions over a 1-month time period. The substances used in the lab that “arm” the T-cells to immunologically fight prostate cancer cells are so-called antigens found on most prostate cancer cells (prostatic acid phosphatase) and a “mouthful” name for certain white blood cell products--abbreviated GM-CSG (granulocyte/macrophage colony stimulating factor). The long and the short of it is that this “vaccine” treatment seems to prolong survival in men with refractory prostate cancer—and at three years after treatment, many more such patients are alive as compared with men not having received this treatment. It’s still not likely a cure, but something to give a man more quality time. Provenge needs to

be given when the hormone-refractory disease 1st appears; the FDA and insurance companies, as well as the producer of this vaccine, require there be some measurable form of disease beyond PSA elevation, e.g., bone metastases—and the patient should not have severely symptomatic prostate cancer, nor shall he have received chemotherapy or be weakened by other therapies recently before the vaccine.

Urologists, by their nature, see a lot of patients with suspected prostate cancer and likely curable malignancies--but far fewer with advanced disease, especially hormone-refractory disease. The newer approaches beyond so-called “cytotoxic chemotherapy” do lend hope to the future for patients whose aggressive brand of prostate cancer will relapse.

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