Endocrine Therapy for Prostatic Cancer Can Replace Orchiectomy and Estrogens

By treating patients who have advanced prostate cancer with a drug that changes endocrine function, physicians in the UT MDAH Department of Urology have produced remissions and promoted well-being in patients who have traditionally had to face the radical side effects of surgical castration and estrogen therapy.

Since January 1983, Andrew C. von Eschenbach, M.D., department chairman, has led a study of the use of buserelin, a luteinizing hormone-releasing hormone (LHRH) agonist, in 22 men between the ages of 59 and 80. All had stage D prostate cancer that had metastasized.

Tests to establish tumor stage and identify metastasis included biopsy, hematologic and biochemical blood assays, urinalysis, radionuclide bone scan, bone radiographs, and lymphangiography or computed tomography (CT) scan, or both. The patients’ general physical condition and endocrine function were evaluated at the beginning and during therapy. Clinical monitoring in collaboration with Naguib A. Samaan, M.D., Department of Endocrinology, and Herbert A. Fritsche, Ph.D., Department of Laboratory Medicine, continues for patients who are still taking buserelin, although entry into the formal study period has ended.

Buserelin has not yet been approved by the Food and Drug Administration for general clinical use, but a similar drug, luprolide (Lupron), is now on the market after being tested at other research centers. It is prescribed by MDAH physicians for some patients with prostate cancer who are not in the buserelin study.

During the first week of therapy, the patients received 1,500 µg of buserelin daily, administered subcutaneously in three doses of 500 µg each, after which the daily dose has been 200 µg.

In a recent interview, von Eschenbach described the results of the study. “Buserelin treatment resulted in a favorable response in all 22 patients,” he said. “Nineteen patients had bone scans that were considered positive for metastatic disease, and 13 of these patients demonstrated improvement. Thirteen patients had lymph node metastases, which regressed in eight patients. Among 17 patients who showed abnormal prostatic acid phosphatase (PAP) secretion, 15 patients improved, and in 12 of these the PAP levels returned to normal.”

Today, nine patients are still in the study. The others suffered relapses and are being treated with chemotherapy. Six patients have died, including two who died from causes other than prostate cancer.

Endocrine therapy, von Eschenbach said, is not curative, nor is any other therapy so far attempted for patients in advanced stages of the disease. But endocrine therapy promotes remissions. It usually alleviates the severe pain of disseminated prostatic cancer in the bones and may relieve problems of urination caused by urethral obstruction, thus improving the patients’ performance status and emotional well-being.

The major advantage of this kind of endocrine therapy, von Eschenbach said, is that buserelin and similar drugs have made orchiectomy and estrogen therapy—which caused gynecomastia in most patients—no longer obligatory. The problems of loss of libido and impotence remain, because all endocrine treatments for prostate cancer exert their effects by withdrawing testosterone from these hormone-sensitive tumors (Fig. 1).

Most Prevalent Cancer in Men

The buserelin results have an importance beyond their numbers, von Eschenbach explained, because cancer of the prostate is an example of the diagnostic and treatment problems clinicians face in dealing with many other forms of neoplasia.

Fig. 1. Mechanisms of endocrine regulation. The prostate is directly affected by androgens produced principally by the testis. These various regulatory mechanisms provide numerous options for endocrine control strategies. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Reproduced with permission from Smith, D. R.: General Urology, 11th Ed. Copyright 1984 by Lange Medical Publications, Los Altos, CA.)
Endocrine Therapy...

continued from page 1

Although it is a disease of aging and rarely occurs in men younger than 50, it is one of the most common cancers in men. About 75,000 cases of prostate cancer are expected to be diagnosed annually, and about 24,000 deaths occur yearly as a result of the disease.

Prostate cancers have differing biologic characteristics and malignant potential, ranging from the slow-growing, confined tumor to the type that grows rapidly and quickly develops aggressive metastasis. In the mid-range is the prostatic tumor that grows slowly for years and then suddenly develops sufficient numbers of cell clones to disseminate to the bones and lymphatic system.

The disease was once considered rare because it is so difficult to diagnose. Compared to the number of prostate cancers diagnosed, three to eight times more cases are not found until patients undergo a prostatectomy for benign disease or during autopsy examinations.

A comparable disease is breast cancer in women, but this occurs earlier in life and is perhaps easier to diagnose at earlier stages because of public and medical education about the disease. There are striking similarities between breast and prostate cancer; for example, both are adenocarcinomas for which hormonal treatments are used, von Eschenbach said.

Because of the difficulties of diagnosing prostatic carcinoma and the heterogeneity of its expression, von Eschenbach and his colleagues have called for a new look at the incidence, development, diagnosis, therapeutic decisions, and evaluation of results—a new effort of which the buserelin study is a part.

Epidemiologic Factors

Epidemiologic studies have shown, he said, that genetic factors (Fig. 2) may play a role because cancer of the prostate is more common among American black men than white men, and because Oriental peoples in their home countries have a lower incidence of clinically diagnosed disease. The latter finding has also led to the suggestion that a diet low in fat and rich in vitamins A and D may play a part in modulating the incidence and virulence of malignant prostatic disease. Environmental factors may have an influence as well, since some studies have linked work in the rubber, textile, and fertilizer industries to higher rates of prostate cancer.

That hormones have a role is certain, although their exact mechanism of action is not known and the responsible endocrine factors have not been identified. The appearance of prostate cancer after age 50 suggests strongly, however, that development of the cancer is related to changes with age in the male endocrinologic environment, when serum testosterone declines and the ratio of estrogen to testosterone rises. The fact that prostatic carcinoma responds to androgen deprivation supports a direct relationship between the tumor and hormonal change.

Pathologic Features

As von Eschenbach explained, the formation of malignant tissue begins in the stem cells of the acinar prostatic epithelium.
Fig. 3. Staging of prostate cancer. Based on extent of tumor, various modifications in the A, B, C, and D types of prostate cancer have been proposed and are currently in use, but the definition of these subdivisions is not uniform. (Reproduced with permission from von Eschenbach, A. C.: Cancer of the prostate, in Hickey, R. C., et al., eds.: Current Problems in Cancer. Copyright 1981 by Year Book Medical Publishers, Chicago.)

Clinical Findings

The tumor has few warning signs because it does not progress in predictable fashion from microscopic disease to regional spread to distant metastasis. That is why, in many patients, symptoms of metastasis may occur before the disease is diagnosed in the prostate gland. Benign disease usually causes obstructive voiding symptoms in older men. Prostate cancer, however, originates in the periphery of the gland and impairs micturition only after the tumor has grown quite large. Most patients do not experience pain on ejaculation or have problems of sexual function but, according to von Eschenbach, hematospermia and hematuria, which may accompany benign hypertrophic hyperplasia, may lead to the detection of unsuspected cancer. The presence of these symptoms in patients older than 50 years should always alert physicians to do a careful assessment.

This is true also for elderly men who may complain of persistent bone pain, which may be multifocal or restricted to the spine or pelvis. A general feeling of illness, fatigue, and weight loss are nonspecific clinical indications of the disease.

When a patient is suspected of having cancer of the prostate, von Eschenbach recommended these procedures:

- Biopsy of the gland with histologic examination of tissue obtained by needle biopsy of the prostate or, at times, by transurethral resection.
- Laboratory studies including complete blood count and serum biochemical profile. Determination of the serum level of acid phosphatase is most important because of the association of elevated levels of serum acid phosphatase and advanced prostatic cancer.
- Radiologic studies including chest radiography, radiographs of the lower spine and pelvis, and radionuclide bone scan.
- Lymphangiography for patients suspected of having nodal disease.
- CT complementary to lymphangiography. Although CT scans do not show intranodal architecture, they reveal enlarged nodes completely replaced by the tumor. Unfortunately, both CT scans and lymphangiograms tend to understage patients with nodal disease.

Fig. 4. Trilogy of the clinical manifestations of prostate cancer. (Reproduced with permission from Johnson, D. E., and von Eschenbach, A. C.: Prostatic carcinoma: A trilogy of clinical expressions. Southern Medical Journal 73(10):1304, 1980.)
Endocrine Therapy...

continued from page 3

![Decision matrix for selecting therapy](image)

**Fig. 5.** Decision matrix for selecting therapy. Tumor grade is correlated with increasing malignant potential, and tumor stage is correlated with increasing tumor burden. TURP, transurethral resection of the prostate. (Reproduced with permission from Smith, D. R.: General Urology, 11th Ed. Copyright 1984 by Lange Medical Publications, Los Altos, CA.)

Treatment

Dr. von Eschenbach summarized treatment, according to the stages of prostatic cancer, as transurethral resection of the prostate; radical prostatectomy; interstitial radiation, external-beam megavoltage radiation, or a combination of the two; endocrine therapy; and chemotherapy (Fig. 5).

He has emphasized endocrine therapy because about one-third of patients already have clinical evidence of metastasis at the time of diagnosis, when total eradication is impossible by currently available techniques.

"Charles Huggins won the Nobel Prize in 1966," he said, "for his discovery in the 1940s of the hormonal mechanisms of prostate cancer, and his work is still the basis of our endocrine treatment. But we are now learning that we can substitute new drugs for the castration and estrogen therapy that can have such severe physical and emotional consequences.

"The disease is so common, yet so often hidden for years, that we must find methods of earlier diagnosis, and more effective treatment for cure. To accomplish this we must learn more about this tumor's biology and behavior."

(Physicians who desire additional information may write Andrew C. von Eschenbach, M.D., Department of Urology, MDAH Box 110, The University of Texas M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030—ED.)

The Cancer Information Service provides up-to-date information and literature about cancer via toll-free telephone lines. Patients can reach CIS at:

1-800-4-CANCER toll-free in Texas
and 792-3245 in Houston

October-December 1985