Advanced Prostate Cancer

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Prostate cancer is the most frequently diagnosed neoplasm in men in the United States and the second leading cause of cancer deaths.[1] Traditionally, advanced prostate cancer was used in reference to patients with bony metastases. Changes in the management and detection of adenocarcinoma of the prostate have altered the very definition of what we consider "advanced disease." Over 50% of patients newly diagnosed with adenocarcinoma of the prostate present with locally advanced or metastatic lesions. This corresponds to stages T3, N+, or M+.[2] Sixty-eight percent of patients with advanced adenocarcinoma of the prostate will respond to androgen withdrawal. This may come in the form of either orchiectomy, estrogen administration, or luteinizing hormone–releasing hormone (LHRH) agonist administration. Unfortunately, one-half of patients with metastatic adenocarcinoma of the prostate will live less than two years.[3] The mean survival of patients presenting with metastatic disease is 1.8 years.[4] Once patients relapse from hormonal control of advanced prostatic carcinoma, few will respond to cytotoxic chemotherapy. Since the introduction of hormonal therapy by Huggins and Hodges in 1941, multiple forms of androgen manipulation have been proposed.[5] The concept of advanced prostatic carcinoma needs to include not only those patients with Stage D-2 (M+), but also those with D0, D1 (N+), C (T-3), a rising prostate-specific antigen (PSA) after radical prostatectomy, and initial high Gleason grade (9 to 10). These patients are all at significant risk of progression and potential death due to prostate cancer.

DIAGNOSIS AND STAGING

As stated before, over one-half of all patients have advanced prostatic carcinoma at the time of diagnosis. Most patients are referred to the urologist for evaluation of a suspicious prostate gland on digital rectal examination (DRE) and/or an elevated serum PSA. Transrectal ultrasound of the prostate (TRUS) along with TRUS-guided biopsy is the preferred method for the diagnosis of adenocarcinoma of the prostate. Biopsies are taken of all hypoechoic regions along with biopsies of palpable nodules. Additionally, systematic biopsies of the peripheral zone are recommended due to the finding of multifocality and nonhypoechogenic properties of some tumors. Fine needle aspiration has also been utilized in many European centers.

Once the diagnosis of adenocarcinoma of the prostate has been made, staging is based on a combination of physical findings including the digital rectal examination and appearance of the prostate gland on transrectal ultrasound. Technetium-99 bone scintigraphy has proven reliable in ascertaining the presence or absence of osseous metastases. Areas of increased uptake can be confirmed with plain films of the area in question. The study is not specific for metastatic lesions, as other processes including degenerative bone and joint processes can also cause increased uptake; however, plain films can usually differentiate osteoblastic metastases from other lesions. CT scanning and MRI have not proven reliable in assessing the status of the pelvic lymph nodes. Transrectal ultrasound (TRUS) is only marginally effective in diagnosing pathologic stage T-2 or T-3 disease, averaging only 60% with wide variation among different institutions.[7,8] Involvement of the seminal vesicles is only accurately diagnosed 38% to 77% of the time by transrectal ultrasound.[6,9] CT scanning is capable of staging the primary prostatic lesion in approximately 67% with a sensitivity for detecting extra-prostatic spread at 50%.[10,11] Magnetic resonance imaging (MRI) is currently being studied for increasing the detection of extra-prostatic spread. Endorectal coil imaging has shown an overall staging accuracy of 68% with a 74% accuracy for staging extra-prostatic disease and a 91% accuracy for detecting seminal vesicle invasion.[12] MRI is obviously limited in its inability to detect microscopic extra-prostatic extension of the tumor.

STAGING OF THE PELVIC LYMPH NODES

Surgical staging of the pelvic lymph nodes remains the gold standard for diagnosing locally advanced adenocarcinoma of the prostate. Most recently, laparoscopic lymphadenectomy has emerged as a minimally invasive method for staging patients with prostate cancer in a select group. These are patients with a PSA greater than 20 ng/mL, Gleason sum 8 or greater, and/or clinical stage of T 2B-C or T-3 disease, in whom the likelihood of lymph node metastases is between 40% to 50%.[13]

PRETREATMENT ASSESSMENT

Once a patient has been diagnosed and staged with advanced prostatic carcinoma, prognostic factors are reviewed, and a recommendation for the most suitable treatment is made. The National Prostatic Cancer Project conducted clinical trials on a broad range of prognostic variables for advanced prostate cancer.[14] The important independent prognostic factors for objective response to treatment were (in order of importance) previous hormone response status, analgesics, pain, elevated acid phosphatase, and anemia. Survival time prognostic factors were (in order of importance) previous hormone response status, anorexia, elevated acid phosphatase, pain, elevated alkaline phosphatase, obstructive symptoms, tumor grade, performance status, anemia, and age. Previous hormone response status was the most important prognostic factor in both analyses.[15] PSA has provided physicians with a much more sensitive and reliable prognostic marker for treatment response in advanced prostate cancer.[16,17] Soloway et al. have combined the initial bone scan with the performance status and PSA in order to integrate the objective and subjective prognostic factors into a reliable system.[18] Stage T-4 prostatic carcinoma is of itself prognostically important, with nearly all men presenting at this stage eventually succumbing to the disease. There is a fairly wide range of variation in survival depending on whether patients present with only nodal spread versus distant metastases. Patients with T-4 M1 disease have a median 30-month survival rate while those with T-4 N1-3 disease have a five-year survival rate.[19,20,21]

Flow cytometric analysis of the DNA content of tumor cells is a relatively new method for assessing the behavior of prostate cancer cells. Aneuploid tumors tend to behave more aggressively and are less likely to respond to hormonal ablation.[22] Ploidy analysis as a separate prognostic indicator is debatable as most high-stage tumors tend to be high Gleason grade and tend to be proportionately more aneuploid. Newer methods of evaluating nuclear shape and morphology along with antigen receptor status are being investigated. Once the diagnosis of advanced prostatic carcinoma has been made and the appropriate staging studies performed, the decision of how and when to treat the patient is made. The decision takes into account the staging, options, and expectations of the patient and the physician.

TREATMENT

In 1941, Huggins and Hodges first reported the effect of hormonal manipulation on metastatic prostate cancer.[5] They realized that either bilateral orchiectomy or diethylstilbestrol (DES) could palliate but not cure patients with advanced prostate cancer.

Table 1. SAFE TREC

S	Status of the tumor (grade, stage, markers)
A	Age, appearance, attitudes
F	Functioning (performance status, sexual, lifestyle, support systems)
E	Expectations (physician, experiences, patient, family response)
T	Therapy (toxicity, other therapies, quality of life)
R	Research (randomized clinical trial, past, present, importance)
E	Efficacy (experience, gain, length)
C	Cost (commitment, time, family cooperation)

SAFE refers to the patients while TREC refers to their treatment plan.

In 1945, Huggins and Scott first reported their attempts at total androgen ablation in patients treated with bilateral adrenalectomy for relapsing prostate cancer.[23]

Due to inadequate Cortisol replacement at that time, survival was short; however, with improvements in steroid replacement along with medications such as aminoglutethimide, which could achieve "medical adrenalectomy," total androgen ablation was achieved.[4,24-25] Nearly 40% of patients with relapse following primary hormonal ablation responded to aminoglutethimide. It inhibits cytochrome P-450–mediated hydroxylation of adrenal steroids; however, concomitant cortisol suppression was required due to increased pituitary production of ACTH. A 60% overall subjective response was reported in these patients; however, supplemental cortisone therapy may have been responsible for some of the symptomatic improvement.[26] The timing of hormonal ablation in patients with advanced adenocarcinoma of the prostate has also been debated since its initial use.[27-28] The VA studies evaluated the effectiveness and toxicity of varying doses of diethylstilbestrol (DES). The most recent update of the second VA study by Byar and Corle suggests that 1 mg DES has a beneficial effect on survival when compared to either placebo, 0.2 mg DES, or 5 mg DES.[29] Regardless of the way one hormonally manipulates advanced metastatic prostate cancer, most patients show disease progression at 1 to 1.5 years with a disease-specific survival rate of two to three years.[19,30] Earlier diagnosis of prostate cancer has resulted in the disease being found in stages: DO, D1 (N+), C (T-3), a rising PSA following radical prostatectomy or initial high Gleason grade (9 to 10). Thus, the question of early hormonal deprivation takes on new importance. Patients with T-3 prostate cancer have been shown to have lower survival rates than those with T-2 disease.[31] Patients with capsular penetration of the pathologic specimen following radical prostatectomy have a 50% incidence of progression within 8 to 10 years following surgery.[32] The vast increase of patients with early advanced disease makes the decision whether or not to institute early hormonal ablation a more common and pressing issue. The update on the second VA Study suggested that early hormonal therapy did have a beneficial effect on survival rate; however, there are studies which support both early and late hormonal ablation.

In the 1980s, luteinizing hormone–releasing hormone (LHRH) analogues were synthesized and used to achieve medical castration. These long-acting compounds suppress testosterone secretion to "castrate levels" by desensitizing the pituitary by altering the normally pulsatile release of LHRH by the hypothalamus.[33] These compounds are relatively safe, their most common side effects being impotence, loss of libido, gynecomastia, and hot flashes.[34] The severe cardiovascular side effects of DES have been avoided with these LHRH analogues. The small percentage of patients who experience short-term exacerbation of their disease initially (the so-called flare phenomenon), can be treated with initial androgen blockade with the non-steroidal anti-androgen flutamide.[35-36] Flutamide has been studied in both monotherapy and combined androgen deprivation studies. Flutamide was not approved as monotherapy for metastatic prostate cancer due to the concern that its effects at the prostatic level could be overcome by endogenous testosterone. Flutamide's major side effects include those of gastrointestinal upset and diarrhea which appear to be dose-dependent.[37] In the 1980s Labrie and Associates reintroduced the concept of complete androgen ablation in patients with advanced prostatic cancer treated with medical or surgical castration along with flutamide.[38,39] While their survival data showed improvement in those patients with complete androgen ablation when compared to historical controls, they were criticized for the lack of a concomitantly matched control group. These studies renewed interest in combined androgen blockade for metastatic prostate cancer. Several large studies have been performed evaluating the combination of LHRH agonist and flutamide versus an LHRH agonist and placebo with resultant improvements in survival rate in the combination group. Crawford et al. reported a 26% improvement in overall survival rate in those who receive combined androgen blockade in 1989.[19] Other large studies have supported the concept of combined androgen blockade with increases in both time to progression and overall survival. In the study by Janknegt et al. analyzing patients with metastatic disease who underwent bilateral orchiectomy with the anti-androgen nilutamide (Anandron) or placebo, time to progression was lengthened from 14.9 to 20.9 months, and survival increased from 30 to 37 months. These results support the Canadian Nilutamide Study.[40,41] The European Organization for Research on the Treatment of Cancer (EORTC) recently reported a seven-month survival rate favoring combination therapy.[42]

Intermittent androgen deprivation has been receiving recent interest. Following initial androgen deprivation, therapy is halted, thus allowing androgen-sensitive tumor cells to repopulate. Androgen deprivation therapy is then reinstituted, thus targeting these androgen-sensitive cells. This concept has been applied effectively to the treatment of other hormonally sensitive cancers such as breast cancer. Protocols involving several forms of combined androgen blockade are under way. An interesting combination for the treatment of advanced prostatic carcinoma involves the use of the five-alpha reductase inhibitor finasteride along with flutamide to decrease the PSA while avoiding the troublesome hot flashes associated with the LHRH analogues.

CHEMOTHERAPY AND PALLIATIVE THERAPY

Historically, advanced prostate cancer has been refractory to cytotoxic chemotherapy and progresses fairly rapidly once becoming hormone refractory, despite all existing modes of therapy.[43-44] Due to the refractory nature of advanced adenocarcinoma of the prostate to standard cytotoxic chemotherapy, some are investigating the efficacy of the antiparasitic agent, suramin, in the treatment of metastatic prostate cancer.[45]

Patients with symptomatic bony metastases can receive significant palliation with external beam radiation therapy to the lesions or with hemibody irradiation.[46-47] A novel approach in the treatment of painful bony metastases involves the use of strontium-89 which is injected intravenously and is handled as a calcium imitator. The radioisotope is taken up and retained in the metastatic sites where it then delivers from 2 to 20 Gy to the localized bone lesion. It

can be repeated at a later date, if necessary, and has been shown to provide effective symptomatic relief in patients with painful bony metastases secondary to hormone refractory adenocarcinoma of the prostate.[48-49]

CONCLUSION

Improvements in the diagnosis and treatment of adenocarcinoma of the prostate have brought about the realization of a large subset of men with early advanced prostatic cancer. It is important to remember that these patients with advanced disease represent a continuum and are therefore constantly changing with respect to their disease, therapeutic options, and lifestyle. Due to this ever-changing milieu involving the patient, his disease, the treatment options, and the physician, a reappraisal of the entire situation is necessary on every visit. With the use of a simple check list, the physician can not only keep track of where the patient lies in the continuum of advanced prostatic cancer, but also make adjustments as necessary to maximize his treatment. The acronym SAFE TREC may be used for such an evaluation (Table 1).

After evaluation of the patient factors, therapeutic options are considered as changes occur in the patient's disease and performance status. Modifications can be instituted and therapeutic options reconsidered. Although we have been aware of the hormonally sensitive nature of advanced prostate cancer since the 1940s, complete androgen blockade on a safe and practical basis has been only more recently developed. Improvement in time to progression and overall survival has been reported with combined androgen blockade; however, investigators are still testing other agents which may improve these responses. STI

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