Editorial

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The Continuing Challenge of Hormone-Refractory Prostate Cancer

Data from 2 prospective randomized trials (TAX 327 and Southwest Oncology Group 9916) using docetaxel-based chemotherapy have demonstrated prolongation of survival in patients with hormone-refractory prostate cancer (HRPC). Nearly 2 years have passed since these data were first presented at the American Society of Clinical Oncology Annual Meeting, and it is time to reexamine the progress and lack thereof since that time.

First, how do we define hormone-refractory disease? This issue has been addressed in a consensus statement,[1] but the simplest and most pragmatic definition of this disease state is "progressive" prostate cancer despite "castrate" levels of testosterone. Castrate testosterone levels have typically been defined as being < 50 ng/dL; progression can occur under a variety of different guises; however, for patients who are sequentially monitored by prostate-specific antigen (PSA) levels, scans, histories, and physical examinations, an increasing PSA level is the first evidence of progression in the vast majority of cases. Most patients today are serially and closely monitored with PSA measurements; consequently, some threshold for PSA change is required to declare progression. This number is not consensus driven at this time; however, a number of clinical trials in HRPC have eligibility criteria that include a PSA increase of ≥ 1-5 ng/mL to ensure that patients with minor PSA fluctuations (for instance 0.11-0.12 ng/mL) are not inappropriately categorized as having progressive disease. Most studies also require that a PSA increase be confirmed with ≥ 1 repeated measurement. Because of the importance of PSA kinetics in determining prognosis (*vide infra*), it is not unreasonable to attempt to establish the rate of PSA increase using several PSA values before secondary intervention.

Secondly, what do we know about the natural history of HRPC? We now know that individuals with radiographic evidence of metastases are distinct from those without. For those with metastatic disease, well-conducted studies from the Cancer and Leukemia Group B have examined prognostic factors and survival: PSA, lactate dehydrogenase, alkaline phosphatase, Gleason score, performance status, hemoglobin level, and the presence of visceral disease have been incorporated into a comprehensive prognostic model predictive of overall survival.[2] However, potential prognostic factors such as vascular endothelial growth factor, chromogranin A, interleukin-6, body mass, cigarette smoking, previous radical prostatectomy, and reverse transcriptase-polymerase chain reaction for circulating PSA messenger RNA have also been implicated by various multivariate analyses.[3-8] For patients with asymptomatic metastatic disease (Abbott-sponsored study M00-211), using a composite endpoint with radiographic and clinical parameters demonstrated that non-PSA progression is driven primarily by bone scan frequency; approximately 50% of placebo-treated patients will have disease progression 90 days after study enrollment when bone scans are done at 90-day intervals.[9]

For patients with PSA progression after castration but without evidence of metastatic disease, fewer data are available, and those data that are available are not necessarily consistent with one another. Retrospective studies from Memorial Sloan-Kettering Cancer Center indicate that the median time to metastases after PSA increase is 9 months and that death follows after a median of 26.5 months.[10] In a second retrospective analysis of HRPC without bone metastases, median survival was 68 months after the initial postcastration PSA increase.[11] Prospective studies of patients enrolled into the placebo arm of a Novartis-sponsored study indicate that the median time to bone metastases after study entry is 30 months.[12] Median time to survival was not reached in this study, but data emphasized the importance of PSA kinetics (velocity) in determining the prognosis of patients with HRPC.

Because a standard treatment for HRPC is now established (docetaxel), one can now ask how this treatment stands in relationship to other (nonstandard) treatments. Secondary hormonal manipulations (ie, ketoconazole, estrogens, glucocorticoids, antiandrogens, and antiandrogen withdrawal) have long been used in HRPC, but because no study with these agents has demonstrated a survival advantage, their potential role is not agreed upon by all. Of note, a study comparing a secondary hormonal manipulation with docetaxel for patients with HRPC failed to accrue, and consequently, the trial was closed prematurely (Eastern Cooperative Oncology Group trial 1899).

Is it possible to enhance docetaxel activity with the addition of another active agent? This is currently an area of considerable discussion and exploration. Large, prospective, phase III trials are now under way using docetaxel with atrasentan, bevacizumab, GVAX®, or calcitriol. Results of these trials are eagerly anticipated. Smaller exploratory trials are now being conducted with a variety of active agents, including docetaxel/samarium-153 lexidronam, docetaxael/ketoconazole, docetaxel/thalidomide/bevacizumab, docetaxel/diethylstilbestrol, docetaxel/satraplatin, and docetaxel/mitoxantrone.

What about patients whose disease has failed to respond to docetaxel therapy? Data in this setting are preliminary but changing rapidly. Combinations of docetaxel/carboplatin have some activity, but the extent of activity is not yet clear.[13] A large registrational trial examining satraplatin/prednisone versus prednisone alone for second-line chemotherapy in HRPC has

now completed accrual (> 900 patients), and the results from this trial are critical for determining the next appropriate step in this setting.

A variety of novel agents are also under investigation. Vaccines such as antigen-presenting cells 8015 and GVAX®, immunostimulants such as granulocyte-macrophage colony-stimulating factor and anti–cytotoxic T-lymphocyte–associated antigen 4, novel chemotherapies such as the epothilones and histone deacetylase inhibitors, monoclonal antibodies to antigens such as prostate-specific membrane antigen and prostate stem cell antigen, as well as variety of signal transduction inhibitors (targeting hedgehog, mammalian target of rapamycin, etc) are currently in clinical trials.

Taken together, many challenges remain in HRPC. Despite the promise of docetaxel-based chemotherapy, optimal sequencing of agents and optimal agents to combine with docetaxel are still undefined. Additionally, the prognosis of patients with HRPC and no radiographically demonstrable metastases remains incompletely understood. Much work remains to be done for this disease state, which represents the final common pathway for the vast majority of patients dying from prostate cancer.

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