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Neoadjuvant Hormonal Manipulation: A Strategy for Chemoprevention Trials

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Abstract Androgen ablation using hormonal manipulation is used extensively in metastatic prostate cancer; however, its use in localized disease combined with surgical extirpation of the gland has not been thoroughly and systematically investigated. The rationale for neoadjuvant therapy stems from the demonstrated effectiveness of androgen ablative therapy in metastatic disease and the high rate of "positive" surgical margins, especially in patients with Stage B_2 disease. In addition, the essentially anecdotal clinical report of Scott and Boyd [1], using endocrine therapy plus radical prostatectomy in patients with Stage C disease, gives 15 year survival results comparable to those obtained by Jewett [2] in Stage 1 patients treated by radical prostatectomy. Finally, experimental observations in the androgen-sensitive mammary tumor (Shionogi) lend support to the concept of neoadjuvant hormonal manipulation.

A pilot study of neoadjuvant endocrine therapy in 55 patients treated at Memorial Sloan-Kettering Cancer Center with 3 months of diethylstilbestrol (DES) (3 mg/day) prior to radical prostatectomy indicates marked reductions in prostate-specific antigen (PSA), although persistent evidence of adverse local tumor features was common. Some patients, however, exhibited evidence of significant downstaging.

Whether or not any alteration in disease progression will accrue from demonstrated local downstaging is, of course, uncertain. However, clinical and laboratory effects of such treatment may provide a means for correlation with subsequent tumor behavior, and may prove useful in treatment decisions. Additionally, a decrease in the number of foci of grade 3 prostatic intraepithelial neoplasia (PIN-3) was noted in a small number of patients. The effects of hormonal and chemical agents on microfocal "early" prostatic cancer and PIN can be readily evaluated by comparing biopsies obtained before the initiation of such therapy with the effects noted in the radical prostatectomy specimen. Thus, potentially useful agents can be readily evaluated in such a neoadjuvant trial and serve as a means of developing potential chemopreventive strategies.

Key words: androgen ablation, chemoprevention, DES, neoadjuvant therapy, PIN, prostate

Radical prostatectomy appears to be effective therapy for localized prostatic cancer, providing the disease is pathologically confined to the prostate. In a highly select group of men (mean age 59 years) presenting with clinically localized prostatic cancer, Gibbons and associates [3] reported an overall 15 year survival rate following radical prostatectomy (55%), equivalent to the expected survival of men in the same age group without prostatic cancer. Jewett [2] reported a similar 15 year survival rate in patients with a solitary nodule (Stage B_1) of prostatic cancer. However, it is of note that no patient with disease involving the seminal vesicles survived 15 years. Although excellent results may be achieved in patients in whom prostatic cancer is confined within the organ, the adverse impact of seminal vesicle invasion [2], positive surgical margins [4,5], and disease beyond the prostatic capsule [6] has been confirmed.

Despite significant improvement in the technology of staging prostatic cancer resulting from the use of serum acid phosphatase, prostate-specific antigen (PSA), bone scans, CT or MRI scans, and transrectal ultrasound, pathologic understaging of apparently clinically localized carcinoma of the prostate remains a major problem [7]. Several reasons for using neoadjuvant preoperative hormonal therapy in these patients are listed below.

1. Most prostatic cancers are significantly understaged, and pathologically more advanced than is clinically apparent.

2. Hormonal manipulation is standard therapy for patients with metastatic prostate cancer; most patients so treated will respond [8], thus demonstrating the hormonal sensitivity of the tumor. This clinical experience also provides considerable evidence that endocrine therapy markedly reduces the volume of the cancer-containing prostate gland.
3. Animal studies in the androgen-sensitive mammary tumor (Shionogi) demonstrate that hormonal manipulation will markedly deplete the tumor stem cell population [9].
4. The currently available serum PSA measurements, transrectal ultrasonography, and improvements in biopsy techniques may accurately identify disease progression earlier. Thus, in evaluating therapies for prostatic cancer, it may no longer be necessary to await survival data in order to judge whether a given treatment or surgical technique will have an impact on the disease.
5. Intriguing indirect data from uncontrolled, essentially anecdotal clinical experiences [10,11] exist to suggest that combined modality therapy has shown some benefit.

The existing data, admittedly non-randomized and retrospective, suggest that in some patients with locally extensive prostatic cancer, the combination of hormonal therapy plus surgical excision of residual non-hormonally sensitive cells may be of benefit to some, but certainly not all, patients. The challenge to the urologic oncologist is to confirm this hypothesis and to devise a means of prospectively identifying those patients likely to benefit from the combined modality approach.

INITIAL STUDIES AT MEMORIAL SLOAN-KETTERING CANCER CENTER

In a small pilot study at Memorial Sloan-Kettering Cancer Center involving 55 surgically staged patients, diethylstilbestrol (DES) (3 mg/day) was administered orally for a minimum of 8 weeks (range: 8–32 weeks) prior to radical prostatectomy [12]. Many of these patients had locally extensive disease that could not have been excised when they were originally seen. Eighteen were initially staged as B_2/B_3; 27 were clinical Stage C; and 10 were clinical Stage D_0 (persistently elevated serum acid phosphatase with no evidence of metastatic disease). After DES therapy, tumor regression permitted attempts at excision in all 55 patients.

That these patients had locally extensive disease was evidenced not only by the high clinical stage but also by the elevated serum PSA levels with a median of 20.4 ng/ml (range 0.6–620). Following DES administration, but prior to radical prostatectomy, the mean serum PSA fell to 0.4 ng/ml (range 0–15.4). Twenty-seven (49%) of the 55 surgically treated patients had no measurable serum PSA level following completion of the three months of DES therapy. Forty-one (75%) of the group had PSA levels below 1.0 ng/ml and all but one of the 55 patients (98%) had PSA levels in the normal range of 0–4.0 ng/ml (Hybritech Assay).

The results of preoperative hormonal manipulation observed thus far in our studies are listed below [7].

1. Although most radical prostatectomy specimens from patients with clinical B_2/B_3, C and D_0 disease in the DES pilot study demonstrated residual extracapsular carcinoma (55%), a few tumors exhibited marked downstaging from the initial clinical stage.
2. In two patients, biopsy-proven seminal vesicle involvement found prior to hormonal therapy could not be confirmed when the radical prostatectomy specimen was examined.
3. Serum PSA or acid phosphatase levels did not predict the pathologic stage of tumor.
4. In a non-study situation, no tumor was found in the pathologic specimen (P_0) from 5%–10% of patients treated with total androgen blockade, despite step sectioning of the entire prostate.

The pilot neoadjuvant study using DES suggested that a "subset" of patients had a pronounced effect from preoperative hormonal therapy. As a result, a second pilot study is now underway utilizing an LHRH analog (Zoladex) plus Flutamide (Eulexin) in patients who are candidates for radical prostatectomy. At the present time we have enrolled 50 of the 63 patients targeted for this study. On the initial

biopsy, tumor ploidy by flow cytometry, proliferation markers (Ki-67, PCNA), and the expression of other phenotypic and genotypic markers (growth factors, multiple drug resistance gene, suppressor genes) will be assessed to determine whether a pattern can be identified which will reliably predict tumor response to the neoadjuvant regimen. The results of this study are not yet available. Upon the completion of this study, we will proceed with a randomized study which has been approved by our Institutional Review Board consisting of three months of total androgen blockade followed by radical prostatectomy, versus radical prostatectomy without hormonal therapy. The current trial, as well as the randomized study, will permit evaluation of various tumor markers in an effort to prospectively identify those tumors which may respond optimally to neoadjuvant hormonal therapy.

NEOADJUVANT HORMONAL MANIPULATION: A POSSIBLE STRATEGY TO ASSESS CHEMOPREVENTIVE AGENTS?

There is a possible additional advantage of neoadjuvant hormonal manipulation. It is well recognized that between 50% and 80% of patients with a proven carcinoma will have one or more microscopic ("early") prostatic carcinomas at the time of pathologic examination of the radical prostatectomy specimen in addition to the index lesion [13]. Additionally, it is also well recognized that precursor lesions of prostatic carcinoma co-exist with frank carcinoma in the majority of glands [14,15]. These lesions, notably prostatic intraepithelial neoplasia (PIN) and/or atypical adenomatous hyperplasia (AAH), may represent precursor lesions of prostatic carcinoma [13–15]. Since microscopic multifocal tumors and PIN are found so frequently in association with prostatic carcinoma, the use of neoadjuvant hormonal therapy provides an opportunity to evaluate the effect of such therapy on these lesions as well as the index lesion. Since the majority of prostatic cancers are slow growing [16], absolute eradication of early cancer or precursor lesions may not be required in order for the strategy to have a beneficial effect. Any agent which would delay the development of obvious malignancy from precursor lesions, or slow the progression of microscopic carcinomas to clinically detectable cancer, may have a significant benefit in prolonging the patient's life span. In a small number of cases examined thus far, neoadjuvant therapy resulting in "complete androgen blockade" appears to have reduced the number of foci of PIN-3 having the same morphological appearance as non- hormonally treated patients, although confirmation of these findings awaits a larger study.

In the absence of any clinical data showing benefit from any chemopreventive agent directed at prostatic cancer, the use of neoadjuvant hormonal therapy provides an opportunity to assess a potential prevention strategy. Agents with a demonstrable effect on microfocal carcinoma and/or PIN in the neoadjuvant setting may be considered for a chemoprevention trial, assuming that toxicity is minimal.

SUMMARY

Admittedly, no definite evidence currently exists that neoadjuvant hormonal therapy of prostatic cancer will either improve surgical curability or extend survival; however, we feel that clinical research in this direction should continue for the following reasons.

1. Although at the present time it is not possible to prove that any patient has benefitted from neoadjuvant hormonal therapy, 5%–10% of patients treated with three months of total androgen blockade were found to have no tumor in the radical prostatectomy specimen. This pathologically documented complete response rate (CR) is equal or superior to results with any currently available chemotherapeutic agent for treatment of prostate cancer.
2. It provides an opportunity to assess predictors of response by comparing clinical and/or phenotypic characteristics of tumors which respond to hormonal manipulation with tumors that apparently are unresponsive. Clinically, it may result in the ability to prospectively identify a "subset" of patients who may benefit from such treatment.
3. Neoadjuvant hormonal therapy may provide a means of assessing agents of potential use in the development of chemopre-

ventive strategies. The alternative—giving large numbers of men a drug of uncertain benefit and following them for the development of clinical cancer—is extremely expensive, time-consuming, and potentially exposes patients to unknown toxicities associated with long-term drug ingestion.

4. Neoadjuvant therapy carries with it little or no risk to the patient, and provides an opportunity to address fundamental biological questions relative to the hormonal sensitivity of prostatic cancer.

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