Prostate Cancer Clinical Trials of the Southwest Oncology Group

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In 1941, Charles Huggins, Clarence Hodges, and R. E. Stevens reported on the beneficial effects of orchiectomy in 21 men with advanced prostate cancer.[1] Fifty-five years later, Southwest Oncology Group (SWOG) investigators were able to confirm, in a 1,387-patient intergroup comparative trial of bilateral orchiectomy with or without flutamide (Eulexin), that we still have nothing better to offer these men. This fact alone should underscore the critical need for well-planned, well-executed clinical trials in prostate cancer. The incidence and death rates continue to rise, and even today too few men are being enrolled in studies designed to alter these statistics.

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Trials in Untreated Metastatic Disease
In the arena of previously untreated metastatic prostate cancer, there are currently two large intergroup trials. The SWOG trial of intermittent androgen deprivation (IAD) assumes that this approach will result in prolongation of androgen dependence, and hence, response to androgen deprivation. This trial has accrued patients at a far slower rate than anticipated. This poor accrual has been attributed to the fact that fewer men present with untreated metastatic disease. However, the true reason is probably multifactorial. There may be disbelief by both investigators and patients that prescribing or receiving less hormonal therapy is better or even equal to continuous androgen deprivation. Unfortunately, there are scant published clinical results supporting this approach.[2,3] Furthermore, the expected improvements in quality of life (QOL) during the time off hormonal therapy must be balanced against the potential decreased QOL resulting from the anxiety of following a rising prostate-specific antigen (PSA) without restarting treatment. In this trial, treatment is not restarted until the PSA is less than 20 ng/mL or there is clinical progression. If accrual does not increase, completion of this trial is in jeopardy. Possible ways to improve accrual would include lowering the PSA required to restart therapy and providing the drugs free of charge. The second large intergroup trial for this patient population is being spearheaded by the Eastern Cooperative Oncology Group (ECOG). This randomized phase III trial of combined androgen blockade (CAB) with or without suramin is based on a pilot trial conducted by the Clinical Pharmacology Branch of the National Institutes of Health showing excellent survival in poor-risk patients.[4] Suramin in this trial is given at a fixed dose and schedule, avoiding the need to closely monitor serum levels. Unfortunately, reluctance by some investigators and patients to add a potentially toxic additional drug to CAB may hinder accrual to this study. In the future, potential trial designs should include the testing of novel agents prior to the initiation of hormonal therapy, as well as the use of concomitant chemotherapy, such as mitoxantrone (Novantrone), to target both the androgen-sensitive and -insensitive prostate cancer cell populations.

Trials in Hormone-Refractory Prostate Cancer
Current or recent trials in hormone-refractory prostate cancer divide between those with primary palliative end points, ie, improved pain control, and those with primary end points of objective response, ie, tumor shrinkage, decline in PSA, and prolonged survival. The serial phase II studies conducted by SWOG have had the same disappointing results as those reported by other investigators, with no new treatment resulting in prolongation of survival.
Although not employed in the SWOG trials, the use of a decline in PSA as a surrogate end point in clinical trials in hormone-refractory prostate cancer is being widely adopted, and is based on analyses demonstrating a correlation between PSA decline and prolonged survival.[5-7] Using this end point, some promising approaches, such as the combination of estramustine (Emcyt), vinblastine, and strontium-89, are emerging[8] and are progressing to the cooperative group setting. Results have been far more encouraging in trials that used QOL as the primary end point. In a recently completed phase III trial of prednisone with or without mitoxantrone, pain reduction was significantly better for the combination-therapy arm.[9] The Cancer and Leukemia Group B (CALGB) conducted a similar large phase III trial with mitoxantrone and hydrocortisone instead of prednisone. Again, patients receiving the combination achieved greater palliative benefit.[10] Nonetheless, in the absence of therapies that prolong survival in hormone-refractory disease, the initiation of serial phase II trials that seek to identify new active agents will remain the backbone of clinical research in this area.

**Trials in Locally Advanced Disease**

As pointed out in this review, locally advanced T3 disease (cT3 and pT3) is becoming the most common stage of prostate cancer. Patients with locally advanced disease are at high risk for recurrence and may benefit from early systemic therapy. SWOG has taken a leadership role with its phase II trials of continuous-infusion fluorouracil and radiation and of neoadjuvant CAB preprostatectomy, as well as its large randomized trial of adjuvant radiation for pT3 disease. The results of these studies are anxiously awaited. The European Organization for Research and Treatment of Cancer (EORTC) recently reported on the results of its randomized phase III trial of radiotherapy with or without concurrently initiated monthly goserelin (Zoladex) continued for 3 years and cyproterone acetate (Androcur) orally for 1 month in patients with T1-4, N0 or NX disease. This trial demonstrated not only better local control but also improved disease-free and overall survival favoring the combined-modality arm.[11]

It is plausible that given the high rate of relapse and occult metastatic disease in this patient population, hormonal therapy alone is adequate to control local and distant disease. This idea leads to the very important National Cancer Institute of Canada (NCIC) trial of hormonal therapy with or without radiation. Facilitated by the GU Global Group of SWOG, this international intergroup trial will assess the possibility of managing locally advanced disease with systemic therapy alone. Similar to therapy for previously untreated metastatic disease, future trials in locally advanced prostate cancer will need to focus on innovative ways to target both androgen-sensitive and -insensitive prostate cancer cells. In addition, correlative science studies evaluating new biologic markers, androgen receptor mutations, reverse transcriptase-polymerase chain reaction, and so on, need to be incorporated into all studies to better identify subsets of patients who are more likely to benefit from different therapeutic approaches.

**Trials in Early-Stage Disease**

Moving to earlier-stage disease, one of the most critical questions being raised is the necessity for local therapy in patients with stage T1 or T2 disease. Many men are currently choosing the watchful waiting approach. The Prostate Intervention vs Observation Trial (PIVOT) was designed to determine the crucial comparative value of intervention (prostatectomy) vs no intervention. It is unfortunate that a third arm of radiation could not have been included. A future intergroup trial is being planned to compare cryosurgery and external-beam radiation. Moving even earlier in the disease process is the 18,000-patient Prostate Cancer Prevention Trial (PCPT). Even if finasteride (Proscar) is not shown to lower the incidence of prostate cancer, this trial will provide a tremendous wealth of information, including the impact of diet and body habitus. It will also provide a tissue and serum bank for future research. This trial accrued patients quickly and demonstrated both the feasibility of and interest in large-scale preventive trials. Future preventive trials under consideration include an assessment of soy supplements and selenium.

**References:**


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