CLINICAL TRIALS Broadcast

In Focus: Prostate Cancer

ECOG 3805: CHAARTED—ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

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Background

Although testing for prostate-specific antigen (PSA) has enabled earlier diagnosis of prostate cancer, it is unclear whether the overall incidence and mortality rates have declined as a result; the most recent data indicate an incidence of approximately 230,000 cases per year with 30,000 deaths per year.[1]

The current treatment for individuals presenting with hormone-naive metastatic prostate cancer is hormone ablation either alone or in combination with antiandrogen therapy, with survival times varying depending on the extent of disease at treatment initiation. PSA testing has resulted in identifying earlier disease that has relapsed after surgery or radiation therapy (ie, prior to disease being seen by imaging modalities). However, it is unclear whether the use of androgen deprivation prior to identification of overt metastatic disease is advantageous. If androgen deprivation is instituted for PSA-only relapse, the earlier diagnosis results in a longer exposure to the toxic effects of androgen ablation, which include osteoporosis. Moreover, the median time from PSA relapse after definitive local therapy to development of overt metastatic disease is approximately 8 years among patients who are observed (ie, if androgen deprivation is delayed).[2] Once hormonal therapy is instituted at the time of development of metastatic disease, the median time to progression is 2–3 years.[3]

Patients with overt metastases are currently treated with androgen ablation therapy alone and followed until disease progression; most patients continue to receive androgen deprivation indefinitely. Of those with metastatic disease, patients with a high metastatic burden ("extensive disease") have a poorer prognosis, with a median time to PSA progression of approximately 10 months and a median time to clinical progression (eg, worsening of bone metastases) of about 14 months.[4,5] The median overall survival among patients with extensive disease is about 24 months, compared to 5 years among patients with minimal disease. Clearly, improved therapeutic options are needed.

Currently, chemotherapy is employed only after hormonal therapy is no longer effective. At this stage, chemotherapy is palliative, and prolongs survival of patients with hormone-refractory disease slightly. Many agents have been evaluated for the treatment of hormone-refractory prostate cancer (HRPC) and only recently has a clear survival advantage been realized with the use of docetaxel (Taxotere, Sanofi-Aventis). Two large phase III trials—Southwest Oncology Group 9916 and TAX327—found that patients with HRPC treated with a docetaxel-based chemotherapy regimen experienced a statistically significantly improved serologic response and overall survival compared to patients treated with mitoxantrone plus prednisone.[6,7]

Eastern Cooperative Oncology Group (ECOG) trial 3805 will determine whether starting chemotherapy simultaneously with hormonal therapy can delay the time to progression without detriment to quality of life in men with extensive disease (defined as four or more bony metastases with at least one involving the appendicular skeleton and/or visceral metastases). All patients will be treated with androgen ablation but daily prednisone will not be administered with docetaxel in order to minimize the toxicity associated with chronic low-dose steroid exposure. It is intended that this approach will not only make the treatment regimen more tolerable, but will also remove prednisone as a confounding variable.

The rationale for this approach is that starting chemotherapy simultaneously with hormonal therapy may be more effective for treating small-volume disease not eradicated by androgen deprivation than it generally is for treating later-stage disease (ie, HRPC), and, additionally, it may prolong the time to progression and thus disease control. However, it may be that early chemotherapy is made less effective by androgen deprivation, which removes cells outside the cell cycle. This issue can only be addressed through a randomized phase III study.

A previously conducted clinical trial evaluating androgen deprivation versus androgen deprivation plus docetaxel-based chemotherapy found a longer time to PSA progression among patients receiving chemohormonal therapy compared with hormonal therapy alone (19 vs 10 months, respectively) among patients with high-volume disease (n=64). At the time of data analysis, there was no improvement in time to PSA progression among patients with low-volume disease (n=50) and no improvement in overall survival in either patient group (personal communication, Randall Millikan).

References

1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin.* 2004;54:8-29.
2. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999;281:1591-1597.
3. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet.* 2000;355:1491-1498.
4. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer [see comments]. *N Engl J Med.* 1998;339:1036-1042.
5. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma [published erratum appears in *N Engl J Med.* 1989;321:1420]. *N Engl J Med.* 1989;321:419-424.
6. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351:1513-1520.
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502-1512.

Objectives

Primary

To evaluate the ability of early chemotherapy to improve overall survival in men commencing androgen deprivation therapy for metastatic prostate cancer

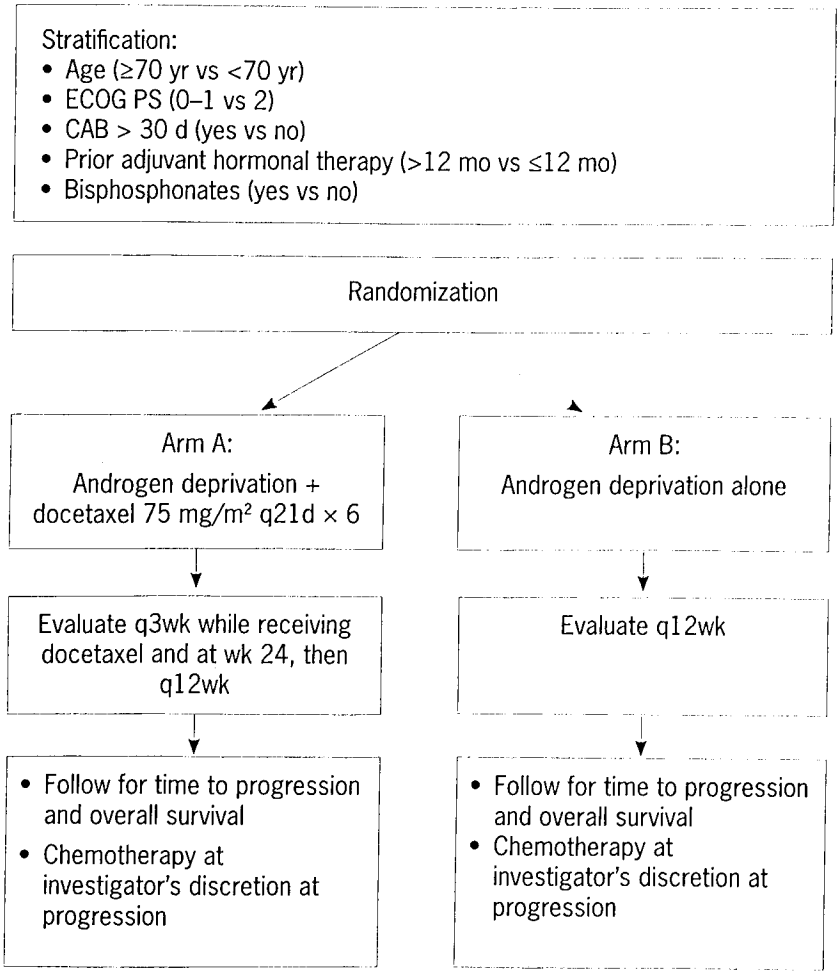
Secondary

- To determine whether early chemotherapy can increase any of the following compared to hormonal therapy alone: time to clinical progression; time to development of hormone-refractory disease; time to serologic progression
- To determine rates of biochemical response at 6 and 12 months in the chemohormonal therapy versus hormonal monotherapy arms
- To determine the frequency of adverse events and the tolerability of chemotherapy combined with hormonal therapy versus hormonal therapy alone
- To determine whether the postulated clinically meaningful increase in disease control is associated with an alteration in overall quality of life
- To determine if PSA changes can serve as a surrogate for clinical benefit from therapy and overall survival

Basic Eligibility Criteria

- Histologically or cytologically confirmed prostate cancer with extensive metastatic disease with plans to start androgen deprivation therapy
- Absolute neutrophil count ≥1,500/mm^2; platelet count ≥100,000/mm^2; total bilirubin ≤ upper limit of normal (ULN); alanine aminotransferase ≤ 2.0 × ULN; creatinine clearance ≥30 ml/min; prothrombin time, international normalized ratio ≤1.5 × ULN (except if on therapeutic anticoagulation); partial thromboplastin time ≤1.5 × ULN (except if on therapeutic anticoagulation)
- More than 4 weeks since major surgery and recovered from all toxicity prior to beginning protocol therapy
- No adjuvant or neoadjuvant hormonal therapy within 12 months prior to starting protocol therapy; no more than 24 months of hormonal therapy total; no evidence of disease at least 12 months after completing adjuvant or neoadjuvant hormonal therapy
- No prior adjuvant or neoadjuvant chemotherapy

Schema



- ECOG performance status (PS) 0–2

Targeted Accrual

568 patients.

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