Materials and Methods: This international program consists of 3 ongoing, randomized, double-blind, placebo controlled clinical trials (trials 23, 24, and 25). Men with localized or locally advanced (T1-T4, Nx/N0, M0) prostate cancer were randomized to receive 150 mg. bicalutamide daily or placebo, in addition to standard care with radical prostatectomy, radiotherapy, or watchful waiting. Primary end points are time to objective progression and overall survival. In this first analysis data from the trials were combined in a single overview analysis according to protocol.

Results: Data are available for 8,113 patients (4,052 randomized to bicalutamide, 4,061 to standard care alone) at a median follow-up of 3.0 years. Treatment with bicalutamide provided a highly significant reduction of 42% in the risk of objective progression compared with standard care alone (9.0% vs. 13.8%, HR 0.58; 95% confidence interval 0.51, 0.66; $P \ll 0.0001$). The overall result was reflected in 2 of the 3 trials (trials 24 and 25) with trial 3 (trial 23) showing a nonsignificant difference at this time. Reductions in the risk of disease progression were seen across the entire patient population, irrespective of primary treatment or disease stage. Overall survival data are currently immature and longer follow-up will determine if there is also a survival benefit with bicalutamide. The most frequently reported side effects of bicalutamide were gynecomastia and breast pain.

Conclusions: Immediate treatment with 150 mg of bicalutamide daily, either alone or as adjuvant to treatment of curative intent, significantly reduces the risk of disease progression in patients with localized or locally advanced prostate cancer. This benefit must be balanced with the morbidity associated with long-term hormonal therapy. Follow-up is ongoing to determine potential survival benefits of this treatment approach.

Commentary

This paper presents the results of studies of more than 8,000 men with localized prostate cancer randomized on three separate trials to evaluate the role of high dose (150 mg) "adjunctive" bicalutamide used in conjunction with either radical prostatectomy or irradiation therapy, or watchful waiting in men with localized prostate cancer. There are few other trials in prostate cancer which either singly or in sum have entered anywhere near this number of patients with prostate cancer. Based on size alone, these trials merit our attention. In view of the known effects of bicalutamide, it is not surprising that the treatment group in these trials appeared to benefit. Treatment with bicalutamide resulted in a 42% reduction in the risk of objective progression compared to standard care—a reduction which was significant at the $P < 0.0001$ level. These results were seen only in the studies of radiation or watchful waiting; there was no significant difference in patients treated adjunctively following radical prostatectomy. Follow-up on these studies is relatively short (2.6–3.24 years) and 75% of the men in the prostatectomy portion of this study had T1 or T2 disease. It seems likely that the failure to demonstrate an advantage of bicalutamide in the prostatectomy study relates to the relatively short follow-up and low event rate in this group of patients. By PSA progression criteria (a criteria of admittedly uncertain value), bicalutamide substantially reduced "failure" in all three studies at P values <0.0001. In this reviewer's opinion, these data contribute to the growing body of evidence provided by studies from the MRC, the ECOG, the RTOG, and the EORTC that early androgen deprivation is beneficial. However, we must remember that this study has not confirmed a survival advantage for high dose bicalutamide. I would take this opportunity to emphasize that the previously mentioned studies by the ECOG, RTOG, and EORTC have all confirmed survival advantage with androgen deprivation used either in conjunction with radiation therapy or radical prostatectomy in the setting of positive nodes and perhaps with more follow-up these studies will as well. It is disappointing that the role of androgen deprivation in prostate cancer remains poorly understood. I hope that the increasing attention to carefully designed studies to test this concept will lead to better definition of the role of early androgen deprivation. This is sharply contrasted with the clear survival benefit of antiestrogen therapy that has been repeatedly demonstrated in the adjuvant therapy of breast cancer. This is yet another example of how breast cancer clinical investigators are far ahead of prostate cancer investigators in addressing issues of substantial importance in our field.

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A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. Jatoi A, Ellison N, Burch PA, Sloan JA, Dakhil SR, Novotny P, Tan W, Fitch TR, Rowland KM, Young CY, Flynn PJ, *Mayo Clinic and Mayo Foundation, Rochester, MN.*

Cancer 2003;97:1442–1446.

Background: Recent laboratory and epidemiologic studies have suggested that green tea has antitumor effects in patients with prostate carcinoma. This Phase II trial explored green tea's antineoplastic effects in patients with androgen-independent prostate carcinoma.

Methods: This study, which was conducted by the North Central Cancer Treatment Group, evaluated 42 patients who were asymptomatic and had manifested, progressive prostate specific antigen (PSA) elevation with hormone therapy. Continued use of luteinizing hormone-releasing hormone agonist was permitted; however, patients were ineligible if they had received other treatments for their disease in the preceding 4 weeks or if they had received a long-acting antiandrogen therapy in the preceding 6 weeks. Patients were instructed to take 6 g of green tea per day orally in 6 divided doses. Each dose contained 100 calories and 46 mg of caffeine. Patients were monitored monthly for response and toxicity.

Results: Tumor response, defined as a decline $\geq$ 50% in the baseline PSA value, occurred in a single patient, or 2% of the cohort (95% confidence interval, 1–14%). This one response was not sustained beyond 2 months. At the end of the first month, the median change in

the PSA value from baseline for the cohort increased by 43%. Green tea toxicity, usually Grade 1 or 2, occurred in 69% of patients and included nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain, and confusion. However, six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity also occurred, with the latter manifesting as severe confusion.

Conclusions: Green tea carries limited antineoplastic activity, as defined by a decline in PSA levels, among patients with androgen-independent prostate carcinoma.

Commentary

Forty-two patients with androgen-independent prostate cancer were treated with green tea. As noted by the authors, multiple studies have suggested both preventive and therapeutic potential from the polyphenols present in green tea. In contrast to other clinical studies in which extracts of green tea have been utilized, this study used "intact" green tea at a dose of 6 g per day. Presumably, though not clearly articulated, the green tea used in this study was all prepared from the same lot and interpatient variation in "potency" of the administered agent was minimized. Standard criteria for antitumor effect in prostate cancer were not met in this study. As pointed out by the investigators, different preparations of green tea or green tea extract as well as longer treatment may yield a different answer. However, for the moment, there is no clinical trial data to support the use of green tea as a therapeutic maneuver in men with androgen-independent prostate cancer.

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Commentary on the next two abstracts follows the second abstract.

Suppression of prostate cancer induced bone remodeling by the endothelin receptor A antagonist atrasentan. Nelson JB, Nabulsi AA, Vogelzang NJ, Breul J, Zonnenberg BA, Daliani DD, Schulman CC, Carducci MA, *Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD.*

J Urol 2003;169:1143–1149.

Purpose: We examined the effects of atrasentan (endothelin-A receptor antagonist) on bone deposition and resorption markers and on bone scan index.

Materials and Methods: This double-blind, randomized, placebo-controlled clinical trial of hormone refractory prostate cancer patients was done at 74 medical centers in the United States and Europe. A total of 288 asymptomatic patients with hormone refractory prostate adenocarcinoma and evidence of metastatic disease were randomized to 1 of 3 treatment groups, namely 2.5 mg atrasentan, 10 mg atrasentan, or placebo administered orally daily until disease progression. The main outcomes measures were changes in bone deposition markers (total alkaline phosphatase and bone alkaline phosphatase) and bone resorption (N-telopeptides, C-telopeptides, and deoxypyridinoline), and in the bone scan index.

Results: At baseline markers of bone deposition and resorption were elevated 1.4- to 2.7-fold above respective upper limits of normal. Subjects receiving placebo experienced a 58% elevation in mean total alkaline phosphatase and a 99% elevation in mean bone alkaline phosphatase ($P < 0.001$), whereas subject receiving 10 mg atrasentan maintained stable mean total alkaline phosphatase and bone alkaline phosphatase values compared with baseline. N-telopeptides, C-telopeptides, and deoxypyridinoline elevation from baseline were consistently less in patients receiving 10 mg atrasentan compared with placebo. Similar trends were observed in subjects who received 2.5 mg atrasentan. Changes in clinical bone scan studies paralleled bone marker changes.

Conclusions: Atrasentan suppressed markers of biochemical and clinical prostate cancer progression in bone and demonstrates clinical activity for hormone refractory prostate cancer.

Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. Carducci MA, Padley RJ, Breul J, Vogelzang NJ, Zonnenberg BA, Daliani DD, Schulman CC, Nabulsi AA, Humerickhouse RA, Weinberg MA, Schmitt JL, Nelson JB, *Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD.*

J Clin Oncol 2003;21:679–689.

Purpose: To evaluate the efficacy and safety of atrasentan (ABT-627), an endothelin-A receptor antagonist, in the treatment of asymptomatic, hormone-refractory prostatic adenocarcinoma.

Patients and Methods: A double-blind, randomized, placebo-controlled clinical trial of hormone-refractory prostate cancer (HRPCa) patients was conducted in the United States and Europe. Two hundred eighty-eight asymptomatic patients with HRPCa and evidence of metastatic disease were randomly assigned to one of three study groups receiving a once-daily oral dose of placebo, 2.5 mg atrasentan, or 10 mg atrasentan, respectively. Primary end point was time to progression; secondary end points included time to prostate-specific antigen (PSA) progression, bone scan changes, and changes in bone and tumor markers.

Results: The three treatment groups were similar in all baseline characteristics. Median time to progression in intent-to-treat (ITT) patients ($n = 288$) was longer in the 10-mg atrasentan group compared with the placebo group: 183 versus 137 days, respectively; ($P = 0.13$). Median time to progression in evaluable patients ($n = 244$) was significantly prolonged, from 129 days (placebo group) to 196 days