Intervention: Patients received six weekly instillations of MMC followed by six weekly instillations of BCG or six weekly instillations of BCG, 3 wk rest, and three further weekly instillations of BCG. Complete responders received three weekly maintenance instillations at 6, 12, 18, 24, 30, and 36 mo in accordance with the initial randomization.
Measurements: End points were complete response (CR) rate at the first control cystoscopy 16-18 wk after start of treatment, disease-free interval, overall survival, and side effects.
Results and Limitations: Ninety-six patients were randomized, 48 to each treatment group. Ten patients were ineligible, and three did not start treatment. In all randomized patients, CR rates on MMC plus BCG and BCG alone were 70.8% and 66.7%, respectively. In 83 eligible patients who started treatment, CR rates were 75.6% and 73.8%, respectively. Based on a median follow-up of 4.7 yr, 25 patients (52.1%) on MMC plus BCG and 22 patients (45.8%) on BCG alone were disease free. Twelve patients stopped treatment due to toxicity: three during induction (two MMC plus BCG, one BCG) and nine during maintenance (three MMC plus BCG, six BCG).
Conclusions: In the treatment of patients with CIS, sequential chemoimmunotherapy with MMC plus BCG had acceptable toxicity. CR and disease-free rates were similar to those on BCG alone and to previous publications on sequential chemoimmunotherapy.
Trial Registration: This study was registered with the US National Cancer Institute clinical trials database (protocol ID: EORTC-30993). ttp://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68869&version=HealthProfessional&protocolsearchid=7920643.

Editorial Comment

Carcinoma in situ (CIS) of the bladder is relatively rare, still an aggressive disease and treatment options are scarce. Intravesical BCG has proven to be better than chemotherapy in several trials. The authors sought to clarify if a combination of both would improve the outcome. Interestingly, they used an unusual statistical method and claimed their study a phase 2 noncomparative trial in which randomization was not done for the purpose of making a treatment comparison but to provide a simultaneous screening of the two treatments. Thus, no p values were given for the end points.

The differences between both treatment arms were small, if any. Side effects were mostly local and not severe. 48.6% of patients had recurred after 5 years on mitomycin C + BCG versus 56.4% on BCG alone.
The authors conclude correctly that the present study and data from the literature do not support the use of sequential intravesical chemotherapy and BCG of CIS.

Furthermore, this study design and conduct shows that if applied carefully, interesting alternatives for large-scale randomized trials do exist.

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Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the combination of avodart and tamsulosin trial

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Background: A 23% relative risk reduction (RRR) in prostate cancer (PCa) was shown in men receiving dutasteride in the 4-yr Reduction by Dutasteride of Prostate Cancer Events study, in whom biopsies were protocol dependent.
Objective: Our aim was to explore PCa risk reduction in men with benign prostatic hyperplasia (BPH) from the Combination of Avodart and Tamsulosin (CombAT) study, in which biopsies were undertaken for cause.
Design, Setting, and Participants: CombAT was a 4-yr randomized double-blind parallel group study in 4844 men ≥ 50 yr of age with clinically diagnosed moderate to severe BPH, International Prostate Symptom Score ≥ 12, prostate volume ≥ 30mL, and serum prostate-specific antigen (PSA) 1.5-10 ng/mL. Men underwent annual PSA measurement and digital rectal examination (DRE), and prostate biopsies were performed for cause.
Intervention: All patients took tamsulosin 0.4mg/d, dutasteride 0.5mg/d, or a combination of both.
Measurements: The primary end point was incidence of PCa. Secondary end points included postbaseline prostate biopsy rates and Gleason score of cancers.
Results and Limitations: Dutasteride (alone or in combination with tamsulosin) was associated with a 40% RRR of PCa diagnosis compared with tamsulosin monotherapy (95% confidence interval, 16-57%; p=0.002) and a 40% reduction in the likelihood of biopsy. There were similar reductions in low- and high-grade Gleason score cancers. The biopsy rate in the groups receiving dutasteride trended toward a higher diagnostic yield (combination: 29%, dutasteride: 28%, tamsulosin: 24%). One limitation was the lack of a standardized approach to PCa diagnosis and grading.
Conclusions: Dutasteride, alone or in combination with tamsulosin, significantly reduced the relative risk of PCa diagnosis in men with BPH undergoing annual DRE and PSA screening. Consistent with the increased usefulness of PSA for PCa detection, men receiving dutasteride had a numerically lower biopsy rate and higher yield of PCa on biopsy.
Trial Registration: Clinicaltrials.gov identifier: NCT00090103 (http://www.clinicaltrials.gov/ct2/show/NCT00090103).

Editorial Comment

This report from a large trial of dutasteride and/or tamsulosin (CombAT) focuses upon the cohort of men in which biopsies were undertaken for cause (suspicion of prostate cancer, PCa).

Men either received dutasteride, tamsulosin or both drugs. Thus, the results of the tamsulosin group may be seen as a control group for the effect of dutasteride. Altogether, PCa was detected in 2.3% in the combination group, in 2.6% in the dutasteride group and in 3.9% in the tamsulosin group. This may not seem impressive, but in pooling the dutasteride arm, there was a 1.5% absolute and a 40% relative risk reduction. Even more interestingly, Gleason sum scores were not significantly different between the groups (means Gleason scores were 6.3 in the combination group, 6.8 in the dutasteride group and 6.7 in the tamsulosin group; p = 0.12). In conclusion, these data underscore the clinical usefulness of dutasteride and even more, an important step toward the reduction of risk for prostate cancer.

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