Flutamide did not prolong survival and increased toxic effects after orchietomy in metastatic prostate cancer


Question
In patients with prostate cancer and distant metastases who had never received antiandrogen agents, would the addition of flutamide to bilateral orchietomy reduce mortality?

Design
Randomised, double-blind, placebo-controlled trial with median follow-up of 49 (placebo) or 50 (flutamide) months.

Setting
Clinical centres in the United States.

Patients
1387 patients (mean age 70 years) who had histologically confirmed adenocarcinoma of the prostate with bone or distant soft-tissue metastases and a Southwest Oncology Group performance status score ranging from 0 (fully active) to 3 (capable only of limited self-care and confined to a bed or chair > 50% of the time). Patients with performance status scores of 3 were included only if pain was the main cause of their functional impairment. Other inclusion criteria were adequate renal function.

Main results
Analysis was by intention to treat. No differences in survival existed between the two groups (Table); the hazard ratio for death for flutamide compared with placebo was 0.91 (90% CI 0.81 to 1.01, P = 0.14). The study had 90% power to detect a 25% difference at the 5% level of significance. Progression-free survival did not differ between groups (median 20.4 mo for flutamide vs 18.6 mo for placebo, P = 0.26). More patients who received flutamide than placebo withdrew because of toxicity (5% vs 1%, P = 0.003) and had ≥ grade 2 diarrhoea (6% vs 3%, P = 0.002) and anaemia (9% vs 5%, P = 0.02).

Conclusion
In patients with prostate cancer and distant metastases who had never received antiandrogen agents, bilateral orchietomy plus flutamide did not prolong survival and was associated with more anaemia and diarrhoea than was bilateral orchietomy alone.

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**Flutamide vs placebo after orchietomy for prostate cancer at median follow-up of 50 months (flutamide) or 49 months (placebo)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Flutamide</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>67%</td>
<td>70%</td>
<td>4% (-3 to 11)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary
Metastatic prostate cancer is a relentless disease that usually leads to a painful death within 3 to 4 years. Treatment used to be based on the androgen-dependent nature of prostate cancer cells and consisted of eliminating only testicular androgen production by either orchietomy or pharmacological means. Total androgen blockade was based on the idea that androgens were produced in both the testis and adrenal glands and involved elimination of both sources of androgen production. Initial studies of total androgen blockade used a combination of pharmacological castration and flutamide and showed a survival benefit for total androgen blockade (1). Not all studies were able to reproduce this result, and a meta-analysis done in 1995 (2) failed to confirm an advantage of total androgen blockade using either surgical or medical castration plus antiandrogen agents.

This large study by Eisenberger and colleagues is well designed with no major flaws and includes the important observation that prostate-specific antigen level is not a useful surrogate marker for survival in patients with metastatic prostate cancer. It adds further evidence against total androgen blockade that uses currently available drugs.

On the basis of current evidence, the decision about treatment of metastatic prostate cancer remains a choice between medical or surgical castration. For many men, the psychological effects of orchietomy make the pharmacological choice more attractive. These issues must be balanced, however, with considerations of side effects and the substantial long-term cost of drugs. The final decision is one in which the patient must play a major and fully informed role.

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References

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