

Androgen blockade in prostate cancer

Sir—We are pleased to see, after such long delays, that the meta-analysis from the Prostate Cancer Trialists' Collaborative Group (PCTCG) of all randomised trials of combined androgen blockade with the pure antiandrogens flutamide and nilutamide was finally published on April 29 (p 1494).¹

Preclinical studies^{2,3} clearly showed that cyproterone acetate has mixed antiandrogenic-androgenic activity. For example, Plante and colleagues³ found that steroidal compounds (ie, chlormadinone acetate, megestrol acetate, cyproterone acetate, and medroxyprogesterone acetate) stimulate androgen-sensitive tumour growth in Shionogi mammary carcinoma, in female mice, while flutamide, a pure antiandrogen, has no stimulatory effect.³ It is not surprising to find in the clinical studies summarised in the meta-analysis, that the addition of cyproterone acetate to castration, not only has no benefit, but, on the contrary, causes a significant increase in the death rate (relative risk=1.13 [SD 0.06], 2p=0.04).

On the other hand, in agreement with previous meta-analyses,⁴ the PCTCG analysis shows a similar significant relative risk (0.92 [SD 0.03], 2p=0.02) in favour of combination treatment of flutamide added to castration, compared with castration alone. A similar relative risk (0.92[0.06]) is found for the combination castration plus nilutamide compared with castration plus placebo.

A major drawback of the PCTCG study, is the pooling of data obtained with fundamentally different antiandrogens. In fact, figure 1 of the PCTCG analysis shows a highly significant lack of homogeneity between the three antiandrogens (p=0.009). This heterogeneity, obviously, is a result of the inclusion of cyproterone acetate. It thus follows that figures 2, 3, and 4 are clearly incorrect and misleading since they include cyproterone acetate. In our definition of combined androgen blockade (this treatment originated at our Institution), only a pure antiandrogen was recommended to achieve a maximal blockade of androgens.⁵

Some other aspects of the manuscript are also surprising. For example, why not only use relative risk of deaths as done in figure 1 and describe the data for each antiandrogen accordingly. Risk ratios provide a better assessment of the magnitude of the

effects of treatment over the whole period of the study than relative risk.

The final conclusion of the meta-analysis should be that combined androgen blockade or the addition of a pure antiandrogen to castration prolongs life and reduces the death rate from all causes by 8% to 10%, relative to castration alone. This difference in all causes of death translates into a 16% to 20% decreased risk of death as a result of prostate cancer. The PCTCG meta-analysis should mark the end of the controversy concerning combined androgen blockade—the treatment clearly shown by this extensive meta-analysis as the best treatment for patients with advanced prostate cancer. The next step is to treat the disease at an earlier stage of the disease when treatment should be more, or hopefully much more, efficient.

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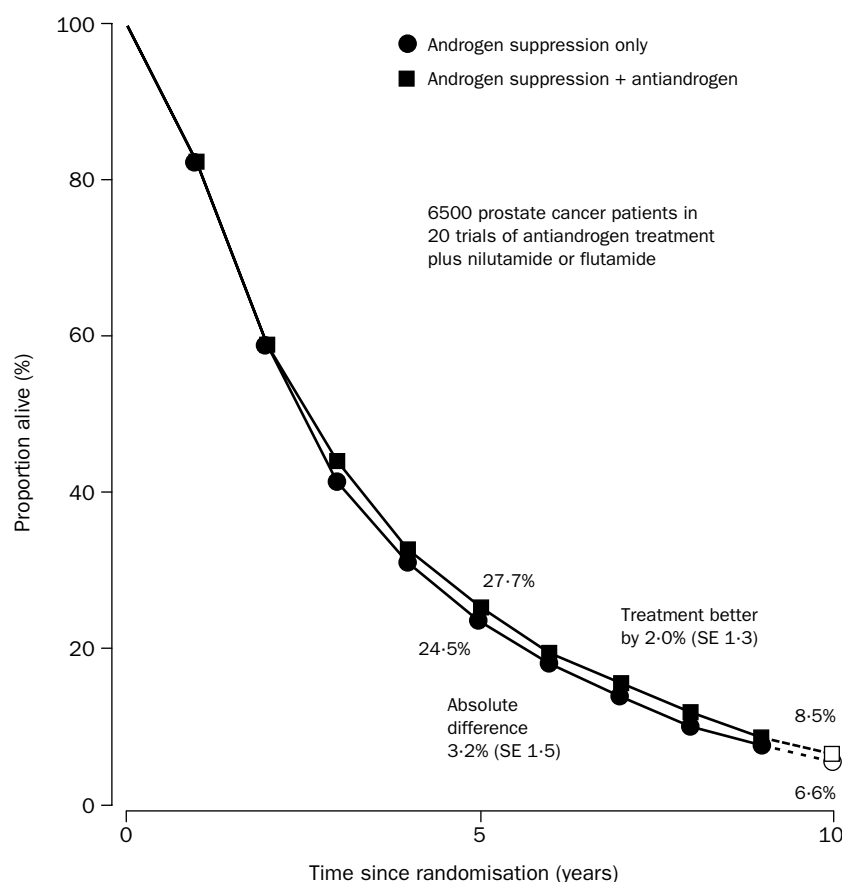
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Authors' reply

Sir—Our overview of randomised trials in advanced prostate cancer showed that the addition of an anti-androgen to castration alone improves the absolute 5-year survival by only about 2% or 3%, with a range of uncertainty that runs from about 0% to 5%. Even if attention were to be restricted only to the results from the 20 studies of flutamide and nilutamide, generating a significant result by ignoring completely the apparently slightly adverse results from the studies of cyproterone acetate, the survival benefit would still not be large (figure).



10-year survival in the randomised trials of nilutamide and flutamide

The difference in 5-year survival would then be about 3%, but with a 95% CI that almost includes zero, and the difference in 10-year survival would be about 2%, with a CI that does include zero. Although we share the hope that it will eventually become possible to identify patients with tumours more responsive to such treatment, the current evidence from randomised trials does not show how to achieve this.

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Pharmacogenetics and antipsychotic drugs

Sir—MJ Arranz and colleagues (May 6, p 1615)¹ draw our attention to the pharmacogenetic prediction of clozapine response. Clozapine has been held up as the best antipsychotic drug for the management of resistant schizophrenia.² However, clozapine has been a difficult drug for both patient and physician. The use of clozapine has been associated with multiple side effects including: agranulocytosis, leucopenia, increase in liver enzymes, neuroleptic malignant syndrome, delirium, seizures, tachycardia, hypotension, myocarditis, cardiomyopathy, and sudden death.²⁻⁵ Clinically relevant side effects occur in 73% of patients treated with clozapine.³ Also, white-blood-cell monitoring is necessary—ie, patients need frequent blood tests. Safer antipsychotic drugs that do not require frequent blood testing are coming onto the market. It is not likely that clozapine will be widely used in the future. When we treat a severe mental illness with a drug that can improve the patient's quality of life, we should not, at the same time, put the patient's physical health and life in danger. I suggest that pharmacogeneticists should focus on drugs that are likely to be used in the future.

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Effects of temozolomide in malignant brain tumours

Sir—I agree with the conclusion drawn by Tracy Batchelor in the April 1 commentary,¹ that patients with high-grade glioma should continue to be enrolled in clinical trials. We are still a long way from an ideal treatment for this deadly disease. However, data from two studies,^{2,3} show that treatment with temozolomide offers health-related quality-of-life (HR-QoL) benefits for patients with recurrent glioblastoma multiforme and anaplastic astrocytoma.

In a phase III study of patients with glioblastoma temozolomide was associated with HR-QoL improvement in several domains, until disease progression was documented by gadolinium-enhanced magnetic-resonance imaging.² In sharp contrast, therapy with procarbazine was associated with deterioration of HR-QoL scores throughout the treatment. The deterioration during treatment with procarbazine was reported, not only by patients whose disease progressed, but also by patients who were judged to have a partial tumour response. Thus, in recurrent glioblastoma, temozolomide is clearly preferable to procarbazine.

In a phase II study of patients with anaplastic astrocytoma treated with temozolomide, improvement in HR-QoL scores was reported until about 4 weeks before documented disease progression.³ These results support the data showing HR-QoL benefits associated with temozolomide treatment for glioblastoma multi-forme from the phase III study.

Temozolomide, as monotherapy, may not be the ideal therapy for high-grade glioma, but it is an effective treatment that offers HR-QoL benefits.

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Cryptococcal meningitis and Cushing's syndrome

Sir—Behzad Razavi and colleagues (April 22, p 1426)¹ describe a man, aged 82 years, who had severe hypokalaemia (2.3 mmol/L), a history of generalised weakness, mood change, weight gain, and diuretic-resistant oedema of his legs. All these signs and symptoms led to the suspicion that the patient had an adrenocortical dysfunction, such as Cushing's syndrome.

It is well established that systematic testing, such as that carried out by the investigators, for an underlying immunocompromised state should be done whenever a patient has an opportunistic infection, such as cryptococcal meningitis. The investigators conclude that a diagnosis of endogenous Cushing's syndrome should be considered when an opportunistic infection occurs. This blanket statement, I feel, may be misleading. Should tests be done to exclude Cushing's syndrome in all patients presenting with opportunistic infections? The answer is no, because estimation of serum cortisol, adrenocorticotropic hormone, and urinary cortisol may not be feasible in all hospitals in developing nations like India; and estimation of hormone concentrations in all patients, without clinical evidence leading to the suspicion of Cushing's syndrome may be unnecessary, exhaustive, and economically non-viable.

The conclusions drawn by the investigators could be modified such that when an opportunistic infection occurs in the presence of a persistent, severe hypokalaemia, the diagnosis of endogenous Cushing's syndrome should be kept in mind. Also, systemic cancer causes an immunocompromised state, as in the patient described, who had an inoperable adrenocortical carcinoma. The compounding effect of secondary hypercortisolism with an underlying primary adrenocortical carcinoma might have led to a severely immunocompromised state and resultant cryptococcal meningitis in this patient.

Also, about 20% of adrenal carcinomas are not associated with endocrine syndromes and are associated with the production of biologically inactive steroid precursors, or are presumably non-functioning.² Hence, the need to thoroughly test for cancer in