

Letters to the Editor

Anti-androgens in treatment of prostate cancer

SIR—The meta-analysis from the Prostate Cancer Trialists' Collaborative Group (July 29, p 265) of 22 randomised trials with 3283 deaths in 5710 patients, reviewed the results of combination anti-androgen therapy in the treatment of prostate cancer. The conclusion was that combination therapy failed to improve survival as compared with monotherapy. This, in our view, is misleading.

The meta-analysis groups together disparate trials contrasting different anti-androgen treatments. The three anti-androgens used have differing endocrinological effects and are not comparable treatments. Cyproterone acetate is a progestational steroid with inherent androgenicity; nilutamide inhibits adrenal hydroxylase activity; flutamide is an anti-androgen that competes directly with testosterone for androgen receptor binding sites. Furthermore, different dosage regimens were treated by the analysis as having similar effects—three cyproterone acetate dosage regimens, three nilutamide regimens, and one flutamide regimen given in combination therapy were considered identical. Both nilutamide and cyproterone acetate had no effect on survival but flutamide led to a 9% reduction in the annual odds of death, which was statistically significant.

The study's overall conclusion is misleading and erroneous. Flutamide is of proven value in the treatment of patients with advanced prostate cancer and helps reduce annual mortality from this disorder.

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SIR—The inclusion of immature studies—some of which were not even planned to measure survival—has decreased the statistical power of the Prostate Cancer Trialists' Collaborative Group's meta-analysis below statistical significance. Moreover, the addition of patients with non-metastatic disease, and pooling of data obtained with two very different classes of anti-androgens introduced heterogeneity to a point where the data of the four prospective, large-scale, double-blind, and placebo-controlled studies performed with flutamide and nilutamide^{1,2} have been diluted sufficiently to mask clearly demonstrated benefits of combination therapy for advanced prostate cancer.

The studies to which we refer have shown the advantages of combination therapy with a pure anti-androgen³ in association with medical or surgical castration, by all objective and subjective parameters studied. Of utmost importance was the finding that the addition of flutamide added, on average, 7.3¹ and 15.1³ months of life. Such results are better even than those obtained for treating breast cancer at a similar stage of the disease. These two studies (under the US National Cancer Institute [NCI] and the European Organisation for Research and Treatment of Cancer [EORTC]) demonstrate statistically that use of an anti-androgen with castration is the treatment of choice to prolong life in advanced prostate cancer.^{1,3,4}

Many of the individual studies included in this meta-analysis were too immature to show statistical significance. Studies reported too early have low statistical power which can lead to a common misinterpretation: that trials which are unable to reject a hypothesis of no effect are providing evidence for no effect. A perfect example of such a problem is the EORTC trial 30853: early reports suggested no significant effect of combination therapy; eventually, however, the prolongation of life in prostate cancer was shown to be 15.1 months.³ In fact, most (if not all) of the data included in this meta-analysis are 3 to 6 years old; the median follow-up is only 40 months; only about 25% of men have died from prostate cancer. This is probably too early to show statistical significance of cancer mortality over the high background mortality from other causes. This possibility is well supported by the survival curve in the Collaborative Group's paper, which shows a small but statistically significant benefit of combination therapy after 2 years but not before. There is little doubt that the analysis planned for 1997 will show different results. Other deficiencies in this meta-analysis also need to be addressed.

The inclusion of non-metastatic disease (with a much longer life expectancy) is not acceptable since it introduces heterogeneity and further delays the significance of the effect on survival. Patients with non-metastatic disease (13% of the meta-analysis) are likely to derive the greatest benefit from combination therapy, but they should be evaluated separately.

Statistical analysis should be done on data collected on the basis of the best science available. It is well known that steroidal and non-steroidal anti-androgens have very different characteristics. Steroidal anti-androgens such as cyproterone acetate possess mixed androgenic and anti-androgenic actions. Such compounds do not block androgens to the same extent as pure anti-androgens such as flutamide and nilutamide. It is not, therefore, scientifically or biologically justifiable to mix the data obtained with all anti-androgens. In fact, cyproterone acetate has never, to our knowledge, shown benefit when added to castration. With the exceptionally high degree of heterogeneity of many of the individual studies included in this meta-analysis, it is not surprising that no significant difference could be detected between the groups of anti-androgens.

Another factor of potential importance in our criticism of this meta-analysis is that patients who have the most advanced disease are those who benefit less from combination therapy, especially in terms of survival. Nevertheless, all such patients benefit from decreased pain and relief of various symptoms throughout a longer duration of response than can be obtained with conventional monotherapy. The NCI and EORTC studies have clearly shown that the survival benefits are mainly obtained for patients with less advanced metastatic disease. Consequently, the inclusion of a sufficiently large proportion of patients who have very advanced disease will proportionally reduce the overall benefit measured on survival. We contend that, for patients with very advanced disease, the duration of the positive response (including improved quality of life) should have been evaluated quite

separately from survival benefit as discerned from trials in advanced, but not very advanced, prostate cancer.

We hold that the present meta-analysis must be considered as being only preliminary, and the deficiencies to which we refer should be widely appreciated. Every effort should be made to correct for immaturity of the data and thereby minimise the risk of misleading interpretations being derived from the meta analysis.

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- 1 Crawford D, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide and prostatic carcinoma. *N Engl J Med* 1989; **321**: 419–24.
- 2 Janknegt RA, Abbou CC, Bartoletti R, et al. Orchiectomy and Anandron (nilutamide) or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993; **149**: 77–83.
- 3 Denis L, Carneiro de Moura JL, Bono A, et al. Goserelin acetate and flutamide vs bilateral orchiectomy: a phase III EORTC trial (30853). *Urology* 1993; **42**: 119–29.
- 4 Labrie F, Dupont A, Bélanger A. Complete androgen blockade for the treatment of prostate cancer. In: de Vita VT, Hellman S, Rosenberg SA, eds. *Important advances in oncology*. Philadelphia: JB Lippincott, 1985: 193–217.

SIR—The study of outcomes in patients given maximum androgen blockade treatments, conducted by the Prostate Cancer Trialists' Collaborative Group, makes a useful contribution to the evolving science of meta-analysis. However, it is unfortunate that the discussion did not point out that, of all the anti-androgens used (flutamide, nilutamide, and cyproterone acetate), only flutamide gave a significant improvement in survival (9%, $2p=0.09$). While the utility of androgen blockade in combination with other agents may need to be further defined, the Collaborative Group's study confirms the results of trials that demonstrate real clinical benefit from androgen blockade, using flutamide and castration. Quality-controlled trials in North America (603 patients)¹ and Europe (327 patients)² have shown that adding flutamide to castration can prolong survival by up to 19 months.

Pooling data from trials of this quality with other studies—smaller in size and not subject to such rigid quality assurance—can only serve to dilute the value of the data rather than reaching an answer closer to the "truth". We stand by our conviction that flutamide combined with castration offers patients with advanced prostate cancer their best chance of survival and good quality of life. This study serves to reinforce that message.

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- 1 Benson RC. Total androgen blockade: the United States experience. *Eur Urol* 1993; **24** (suppl 2): 72–76.
- 2 Denis L, Whelan P, Carneiro de Moura JL, et al. Goserelin acetate and flutamide vs bilateral orchiectomy: a phase III EORTC trial (30853). *Urology* 1993; **42**: 219–30.

Authors' reply

SIR—In advanced prostate cancer, no significant survival advantage was found on systemic review of 22 randomised trials that compared conventional castration versus maximum androgen blockade (ie, castration plus an anti-androgen). In ten of these trials the anti-androgen tested was flutamide, in eight it was nilutamide, and in four it was

cyproterone acetate. When attention was restricted just to the ten flutamide trials there was still no conventionally significant survival advantage ($2p=0.09$). Despite randomisation of more than 3000 patients in these ten trials, most of whom have already been followed up until death, the median survival is almost the same with and without flutamide. This finding argues strongly against the suggestions of your various correspondents that flutamide might well improve survival by 7, 15, or "up to 19" months. Unfortunately, they seem to have cited only the trials that happened to favour flutamide (and, even within those selected few trials, the published differences in median survival are actually only 3–7 months). Had they, instead, cited only the unfavourable trials—such as, for example, the Australian multicentre study¹—their conclusions would have been opposite, and had they cited all the relevant trials their conclusions should have been that there is no significant survival advantage (so long as they avoid describing $2p=0.09$ as being "significant").

In choosing to emphasise the findings from only a few selected studies, rather than these overall conclusions, your correspondents may have been overlooking the large distortions that can be produced by unduly selective emphasis on particular parts of the evidence. This is particularly so when, as here, the results for survival show no significant heterogeneity between the 22 different anti-androgen trials, or between flutamide and the other two anti-androgen drugs, or between the ten different flutamide trials (in five of which the flutamide group had somewhat worse survival than the controls).

Thus, results from the randomised trials do not provide reliable evidence that survival is prolonged, and none of Labrie and Crawford's more specific concerns invalidate this conclusion. In particular, because appropriate methods of analysis (life table techniques) were used, the inclusion of some immature studies does not bias the survival curves. Failure to improve survival significantly occurred despite the fact that the large majority of both early and late deaths must have been from prostate cancer (indeed, comparison with normal life expectancy shows that about half the randomised patients had already died from the disease). The overall results would be unchanged by restricting them to patients who already have overt metastases. Also, the overall findings are much the same whether the three different anti-androgens are considered separate, or together. Turning to other outcomes, in some patients the symptoms of prostate cancer are indeed relieved somewhat more rapidly if anti-androgens are used, but there is little change in the eventual proportion who gain relief from their cancer symptoms, and drugs such as flutamide often have considerable side-effects.²

We agree, however, with Labrie and Crawford's final point, that the present mortality analyses are preliminary; another cycle of this collaboration is planned for 1996–97 and we very much share the hope that the trial results then available will, unlike those currently available, demonstrate at least some small improvement in survival beyond year 5.

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- 1 Marshall V, Thompson P, Raghavan D, Zalberg J. First report of Australian multicenter randomized prostate cancer trial: flutamide does not add to the effect of orchiectomy for metastatic prostate cancer. *Proc Am Assoc Cancer Res* 1992; **33**: 1315.
- 2 Wysowski DK, Freiman JP, Tourtelot JB, Hortong ML. Fatal and nonfatal hepatotoxicity associated with flutamide. *Ann Intern Med* 1993; **118** (11): 860–64.