Adjuvant treatment with tamoxifen

Side effects may have been overstated

EDITOR,—Use of clinical announcements by the National Cancer Institute to influence policy on the European side of the Atlantic¹ is a dubious and previously discredited process, and this would not be the first time that such an announcement has caused distress on this side of the Atlantic. The data cited in these "alerts" are unpublished and not subjected to peer review and (from what we can glean from the limited amount of information available) are based on so few events after randomisation as to make any statistical analysis highly unreliable.

R D Bulbrook repeats the accusation made on television that tamoxifen has 40 side effects.¹ We would be the last to state that tamoxifen is free of side effects, but most of these so called side effects are anecdotal or identical with those observed among patients taking placebo.² The fact remains that compliance with tamoxifen as adjuvant treatment and even in a prevention trial is extraordinarily good.² Furthermore, in the Cancer Research Campaign's trial with over 3000 patients randomised between two years and five years many patients are refusing randomisation at the two year point because they feel well and wish to continue taking the drug. Bulbrook also selectively cites one trial questioning tamoxifen's role in premenopausal women but ignores the much larger body of evidence indicating reduced recurrence rates and contralateral tumours in premenopausal women.^{3,4}

Bulbrook goes on to describe the decision of the state of California to register tamoxifen as a carcinogen. This is absurd, particularly as tamoxifen cannot be considered to be an environmental hazard. Simple one line classifications are not scientifically useful for pharmaceutical products, which are taken for their benefits, and

serve only the interests of tabloid journalists and pressure groups with political agendas.

For the sake of prudence we advise all women taking tamoxifen of the possible side effects, including endometrial cancer. Many epidemiologists, however, have raised serious doubts about the evidence associating tamoxifen with an excess of endometrial cancer. The opportunity for ascertainment bias is considerable. Tamoxifen's true side effects produce gynaecological symptoms and artefactual ultrasonographic changes suggestive of endometrial thickening. This then leads to biopsy, which provides the opportunity for detection of latent endometrial cancer, which might never express its malignant potential in the woman's lifetime.⁵ If this is the case then to accuse tamoxifen of causing endometrial cancer is equivalent to suggesting that testing for prostate specific antigen causes prostatic cancer.

MICHAEL BAUM

Chairman, breast cancer trials coordinating committee,
UK Coordinating Committee on Cancer Research

JACK CUZICK

Chairman,
international breast cancer intervention study working party

International Breast Cancer Intervention Study

Coordinating Centre,
PO Box 123,
London WC2A 3PX

1 Bulbrook RD. Long term adjuvant therapy for primary breast cancer. *BMJ* 1996;312:389-90. (17 February.)

2 Powles TJ, Hardy JR, Ashley SE, O'Brien ME, Tidy VA, Treleavan J, et al. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. *Breast Cancer Res Treat* 1994;31:73-83.

3 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Systematic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992;339:1-15.

4 Fisher B, Redmond C. New perspective on cancer of the contralateral breast: a marker for assessing tamoxifen as a perspective agent. *J Natl Cancer Inst* 1991;83:1278-80.

5 Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser M. Detection of endometrial carcinoma and hyperplasia in asymptomatic women. *Obstet Gynecol* 1984;64:1-11.

Local research ethics committees should review their approval of prevention trial

EDITOR,—R D Bulbrook's editorial discusses who should take tamoxifen and for how long.¹ The British aTTom (adjuvant tamoxifen treatment offer more) trial aims to recruit up to 20 000 women with primary breast cancer. Many of these women could receive at least seven years' treatment with tamoxifen—two years more than the National Cancer Institute considers routinely advisable for American women on the basis of current evidence. Women invited to take part in this trial will need full and frank information in the light of growing concern about the risks of long term treatment with tamoxifen, which include endometrial cancer and, possibly, gastrointestinal cancer. Some subgroups of women with a good prognosis are not likely to benefit from tamoxifen, and there is a danger that a conflict of interest may arise between the need to individualise treatment for patients or to enter them into a trial that requires large numbers to provide a quick, reliable answer.

Bulbrook's remarks have important implications for the chemoprevention trial in healthy women deemed to be at higher than usual risk of breast cancer. Since the prevention trial was first proposed many more data have become available on the risks associated with the use of tamoxifen, particularly among premenopausal women. A recent study found that women exposed to tamoxifen for more

than five years when they were premenopausal or perimenopausal were at higher risk of developing endometrial cancer than women exposed after the menopause.² Tamoxifen also causes bone loss in premenopausal women and is less effective in preventing contralateral breast cancer in premenopausal than postmenopausal women. Perhaps, in the light of this information, the time has come for the local research ethics committees that approved the prevention trial to review the grounds on which they did so.

CATHERINE READ
Science writer

33 Cockshutt Road,
Beauchief,
Sheffield S8 7DY

1 Bulbrook RD. Long term adjuvant therapy for primary breast cancer. *BMJ* 1996;312:389-90. (17 February.)

2 Sasco AJ. Tamoxifen and menopausal status: risks and benefits. *Lancet* 1996;347:761.

Recruitment into studies assessing optimum duration of treatment must continue

EDITOR,—R D Bulbrook's editorial prejudices the issue of the duration of tamoxifen as adjuvant treatment for breast cancer.¹ Its conclusions are based on an announcement by the American National Cancer Institute that the national surgical adjuvant breast and bowel project trial B-14, which compared five with up to 10 years of tamoxifen, was to be stopped on the advice of the data monitoring committee. On the basis of unpublished data from just over 1500 randomised patients from this and a Scottish study² the National Cancer Institute concluded that its trial would not show a benefit from continuing tamoxifen beyond five years. Although there was a trend for women to do worse if they continued tamoxifen beyond five years, the number of events was small and no significant differences were observed. With over half a million women diagnosed as having breast cancer every year, it does not make sense to base recommendations for such a large cohort of patients on non-significant results from two such small studies.

The United Kingdom Coordinating Committee on Cancer Research is presently undertaking the national aTTom (adjuvant tamoxifen treatment offer more) study, which seeks to recruit women with breast cancer who have been taking tamoxifen for any period (but at least two years is recommended) and for whom there is uncertainty whether they should continue. Such women are randomised to stop taking tamoxifen or to continue to take it for at least a further three years. All that is required to enter a patient is one (free) telephone call to the trial centre (0800 371969). Follow up is through national records of dates and causes of death, and second cancers are monitored through national cancer registries. The aim of the aTTom study, together with its international counterpart, Atlas, is to randomise the 20 000 women needed to define the optimal duration of tamoxifen treatment.

We wish to protest at Bulbrook's misrepresentation of the aTTom trial, which stems from a flawed interpretation of the small amount of evidence currently available on women who have taken tamoxifen for over five years. The statements expressed will raise alarm among women with breast cancer and doctors in general and, more importantly, among those who are already par-

Advice to authors

We receive more letters than we can publish: we can currently accept only about one third. We prefer short letters that relate to articles published within the past four weeks. Letters received after this deadline stand less chance of acceptance. We also publish some "out of the blue" letters, which usually relate to matters of public policy.

When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Wit, passion, and personal experience also have their place.

Letters should have fewer than 400 words and no more than five references (including one to the *BMJ* article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters should be typed and signed by each author, and each author's current appointment and address should be stated. We encourage you to declare any conflict of interest.

Please enclose a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

Letters will be edited and may be shortened.