Eur J Cancer, Vol. 26, No. 3, pp. 315–319, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Haemostatic Changes During Hormone Manipulation in Advanced Prostate Cancer: A Comparison of DES 3 mg/day and Goserelin 3.6 mg/month

LAWRENCE A. EMTAGE,* JOHN GEORGE,† BRIAN J. BOUGHTON,† CATHERINE TRETHOWAN* and GEORGE R.P. BLACKLEDGE*

**West Midlands Cancer Research Campaign Clinical Trials Unit, Department of Medicine, Queen Elizabeth Hospital, Birmingham B15 2TH, U.K. and †Department of Haematology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, U.K.*

Abstract—*Two hundred and fifty patients were entered into a randomized clinical study to compare the effectiveness of goserelin (Zoladex) in depot formulation with diethyl stilboestrol in locally advanced or metastatic prostate cancer. In 22 patients from the two arms of the study regular assessments were made of the effect of these hormone treatments on the haemostatic system. Selection of those patients with no recent surgical intervention and those on no drugs liable to interfere with the haemostatic mechanism was done at entry, in order to remove bias and achieve comparable groups. Baseline comparison of the two treatment groups showed no difference in clinical or biochemical measures of disease extent or activity, including serum prostate specific antigen (PSA) levels. There was a significant fall in plasma antithrombin-III (AT-III) activity in the DES treated group both from baseline and compared with the goserelin group. This effect commenced within 1 month and was maintained until monitoring ceased at 12 months. There was also a significant increase of fibrinolytic activity in the DES treated patients compared with those on goserelin. No divergence between the two treatment groups was seen in any other haematological parameters at baseline or on follow-up. A single AT-III estimation was also performed on a larger group of 74 patients at median follow-up time of 17 months (range 3–24). This confirmed the difference noted in the original study group. In the main study thrombotic episodes were noted in 13/126 patients treated with DES and 0/124 treated with goserelin ($P < 0.001$). These findings suggest that lowered AT-III is the major factor through which DES affects the coagulation mechanism, and that no such effect is seen with goserelin treatment despite an equivalent therapeutic efficacy.*

INTRODUCTION

THE INCIDENCE of thrombotic complications in patients with advanced prostate cancer is increased by the use of oestrogen therapy [2–4]. Decreased AT-III levels are associated with an inceased risk of thromboembolic events [5, 6] and oestrogen therapy has been reported to decrease AT-III levels [7]. We have studied the effects of depot goserelin (Zoladex) 3.6 mg monthly and diethyl stilboestrol (DES) 3 mg/day on several aspects of platelet function, fibrinolysis and coagulation in patients selected at random from a larger trial of advanced prostate cancer comparing the two forms of hormone manipulation.

Accepted 16 November 1989.
Correspondence to: Dr G. Blackledge, Queen Elizabeth Hospital, Birmingham B15 2TH, U.K.

PATIENTS AND METHODS

Twenty-two patients entering a multicentre randomized trial comparing goserelin 3.6 mg depot with DES 3 mg/day were selected for further study (see below) after randomization to the main trial. All cases had biopsy proven, locally advanced or metastatic prostate cancer, and the main exclusions were other neoplastic disease or serious pre-existing cardiovascular disease. These patients were not on any form of regular analgesia or beta blockade, and all but three had been allowed to recover from a surgical procedure, usually transurethral prostatic resection, for at least 2 weeks prior to testing (Table 1). These three had their first assessment 6, 7 and 8 days following surgery respectively, and as their trial entry data showed no difference from the rest of the group, they have been included in the analysis.

Table 1. *Patient characteristics* ( ) = % *unless stated otherwise*

	Goserelin	DES
Median age (and range)	71 (57–81)	75 (53–86)
Current smoker	5/11 (45.5)	4/11 (36)
Performance score normal	10/11 (91)	11/11 (100)
Cardiovascular disease	4/11 (36)	3/11 (27)
Tumour area (mean and confidence intervals)*	22.9 (15.8–29.9)	22 (14.8–29.3)
Primary tumour stage T4	4/11 (36)	3/11 (27)
Primary tumour stage T3 or less/MO	1/10 (10)	2/11 (18)
High acid phosphatase	8/11 (72.7)	4/11 (36.4)
High alkaline phosphatase	4/11 (36.4)	7/11 (63.6)
PSA greater than 100 μg/l	5/11 (45.5)	8/11 (72.7)
Histology		
Good	2	1
Moderate	5	6
Poor	3	3

Median time from TUR prostate to first test
n = 17 (five cases were diagnosed by needle biopsy).
Median 32 days (range 6–709).
*Tumour area = the product of width × length of the prostate as assessed by digital rectal examination.

Age range for the whole study group was 53–86 years; median 72. All patients gave informed consent for both studies, and underwent haematological analyses at baseline, 1 month, 3 months and 1 year. At each visit the recent analgesic intake of the patient was noted, and there were no protocol violations.

Platelet count was estimated using a Coulter Model S+IV analyser (Coulter Electronics, Luton). ADP-induced platelet aggregation threshold and spontaneous aggregation were measured as previously described using a PAP-4 platelet aggregometer (Biodata Corporation, Hatboro, PA) [8, 9]. All platelet aggregation tests were performed within two hours of venepuncture. Beta-thromboglobulin was estimated by a radioimmunoassay kit (Amersham International plc, Amersham). Euglobulin lysis was determined by the method of Buckell [10], with the results reported as units of fibrinolytic activity [11]. AT-III and α_2 antiplasmin activity were measured by chromogenic substrate assays using kits supplied by Immuno Diagnostika (Vienna) and Kabivitrum (Stockholm), respectively. Immunological fibrinogen and von Willebrand factor antigen were estimated by the Laurell immunoelectrophoretic technique [12] using antisera supplied by Dakopatts, Copenhagen. Clottable fibrinogen was measured by the method of Clauss [13] using a kit supplied by Immuno Diagnostika. Factor VIII coagulant activity (F.VIII:C) was determined by a modified two-stage technique [14] within 2 h of venepuncture. Serum FDP was measured using a latex agglutination method (Thrombo-Wellcotest, Wellcome Diagnostics, Dartford).

Some data was lost due to missed appointments (five cases), treatment withdrawal (two cases) and on-study death (one case). The assessment of AT-III in a further 74 patients in the main study was performed at median follow-up of 17 months (range 3–24 months). Statistical analyses were carried out using the Mann–Whitney and chi-squared tests.

RESULTS

Baseline characteristics

The two treatment groups were well matched in terms of age, disease extent, histology, performance status, prior history of cardiovascular disease and smoking (Table 1). This study group also compared well with the whole study group in terms of these parameters. Over the study period, 13 cases showed a partial response to therapy in terms of either primary tumour shrinkage or lessening of the number of bone metastases on follow-up bone scans, seven were classed as progressing and two were unassessable as only baseline data was available. There was no statistically significant difference in response between the two therapy groups.

Of the 12 haematological parameters tested, only β-thromboglobulin showed a significant difference at baseline in the two treatment groups (P = 0.002), being above the normal range in 7/11 goserelin treated cases. This difference was lost within 1 month of beginning treatment. Both patient groups presented with slightly elevated F.VIII and fibrinogen levels, probably reflecting the disease process. Mean factor VIII:C levels on presentation were 1.60 ± 0.60 iu/ml and 1.89 ± 1.01 iu/ml in the goserelin and DES groups respectively (n.s.). Four patients in the goserelin group and three in the DES group had baseline F.VIII:C levels in excess of 2.0 iu/ml (normal range 0.5–2.0).

Follow-up

Only two parameters showed significant changes on DES therapy. AT-III showed a statistically significant fall from baseline at 1 month ($P = 0.03$). This effect was also noted at 1 and 3 months ($P = 0.001$, 0.008) (Table 2) and at 1 year ($P = 0.027$), when compared with the goserelin group. Fibrinolytic activity, as measured by the euglobulin lysis test, was significantly higher in the DES group at 3 months ($P = 0.01$) and at 1 year ($P = 0.03$) (Table 2).

AT-III measurements in the main trial patients

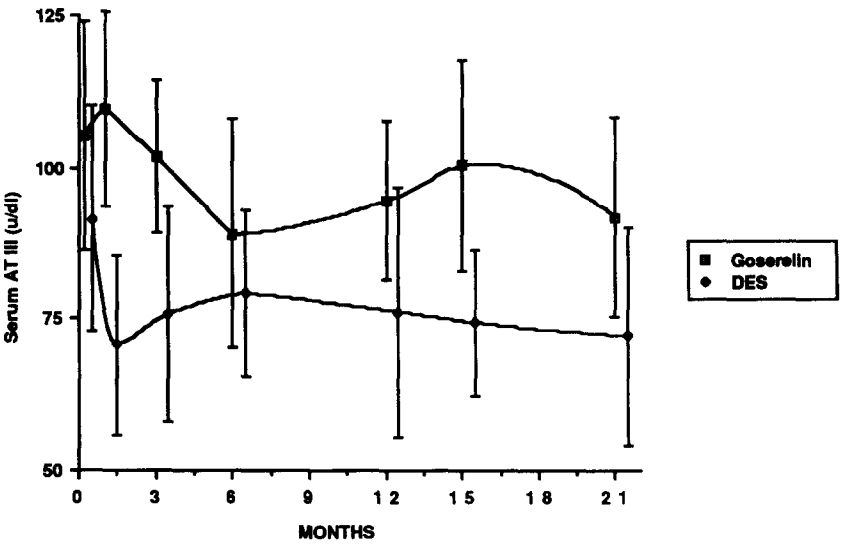
A single AT-III estimation was also performed on a larger group of 74 patients at median follow-up time of 17 months (range 3–24). This confirmed the difference noted in the original study group (Fig. 1). Thrombotic episodes were noted in 13/126 patients treated with DES and 0/124 treated with goserelin ($P < 0.001$). These were myocardial infarction (2), pulmonary embolus (1), cerebrovascular accident (2), transient ischaemic attacks (3), deep venous thromboses (4) and peripheral arterial thrombosis (1).

DISCUSSION

The main randomized open study was set up to test the efficacy and safety of goserelin compared with DES. We report the results of a study of a subgroup of these patients using a range of coagulation tests to monitor changes during treatment. The study group was well matched in terms of baseline

Table 2. Mean (± S.D.) levels by treatment group and probability of equivalence (Mann–Whitney test)

	Plasma antithrombin III activity (%)			
	Entry	1 Month	3 Months	1 Year
Goserelin	105.2 (18.8)	109.6 (16.1)	101.5 (13.4)	93.4 (16.0)
DES	91.5 (18.6)	70.6 (14.9)	78.2 (17.3)	71.4 (16.0)
P value	0.107	0.001	0.008	0.027
	Euglobulin lysis (units of activity)			
	Entry	1 Month	3 Months	1 Year
Goserelin	52.2 (26.6)	46.9 (12.9)	38.6 (11.7)	40.2 (15.7)
DES	61.5 (52.4)	82.4 (57.5)	86.7 (42.2)	77.0 (35.3)
P value	0.974	0.167	0.01	0.03



N								
goserelin	11	9	14	8	14	13	14	
DES	11	7	13	7	9	7	6	

Fig. 1. Mean (± S.D.) antithrombin III values in the main study group.

characteristics, both with the main trial group and within each treatment group. This was important, because disease extent appeared to have some effect on baseline values.

The chromogenic AT-III assay used in this study was similar to that used by Varenhorst *et al.* [15]. The decrease in AT-III activity was rapid and prolonged with DES therapy at a dose of 3 mg/day. Although no clinical thrombotic event took place in either treatment group in this sub-population, it was felt that the AT-III levels as low as 40% of normal on DES were sufficiently low to predispose to such an event. Changes in AT-III are therefore the most probable causative factor in the thrombotic events which caused a significant proportion of patients to be withdrawn from DES therapy in the main study, despite a significant increase in fibrinolytic activity in patients on DES therapy. A similar effect has been observed by Walther *et al.* [1] and was attributed to an increase in tissue plasminogen activator (t-PA). We did not, however, measure t-PA in this study. None of the other parameters studied showed a significant change on either treatment. The increased ADP induced platelet aggregation reported elsewhere with oestrogen treatment [16] was not seen in either treatment group in this study. Prostate cancer itself caused significant changes in several of these parameters, in particular increased fibrinolytic activity [1, 17]. It was notable that both treatments tended to normalize these levels, with the exception of AT-III and euglobulin lysis in those on DES. Baseline AT-III and euglobulin lysis levels were not grossly abnormal in either treatment group, and so it cannot be said that disease related levels were further adversely affected by DES treatment.

We conclude that of 12 haematological variables studied, the only one to show a profound and persistent fall on therapy was AT-III, which was very sensitive to oestrogen therapy. Although this relationship between oestrogen therapy and alteration of AT-III levels has been reported previously [18], it is of note that the LH-RH agonist goserelin had no effect on the components of the coagulation system that were measured in this study, confirming earlier observations by Varenhorst *et al.* [19]. These observations suggest that the highly significant difference in thrombotic episodes seen in the main trial (13/126 for DES and 0/124 for goserelin) can be explained by the effect of DES on the coagulation system.

Criticism could be levelled at the main trial that the dose of DES was higher than necessary. Whilst lower doses of DES might have the same antitumour efficacy, alterations in the clotting mechanisms would still occur. Even though the therapeutic efficacy of the two treatments appears similar, the absence of thrombotic complications with goserelin and its complete lack of action on the coagulation system would suggest that it is superior to any dose of DES, and is thus the preferred medical treatment for advanced prostate cancer.

Acknowledgements—We should like to thank all the urologists who contributed patients to this trial, and to the staff of the West Midlands Cancer Research Campaign Clinical Trials Unit for their assistance. We acknowledge the support of ICI Pharmaceuticals in carrying out this study.

REFERENCES

1. Walther PJ, Gore M, Pizzo SV. Increased releasable vascular plasminogen activator and a bleeding diathesis. *Am J Med* 1984, **77**, 566.
2. Blackard CE, Mellinger GT, Gleason DF. Treatment of stage I carcinoma of the prostate: a preliminary report. *J Urol* 1971, **106**, 729–733.
3. The Veterans Administration Co-Operative Urological Research Group. Treatment and survival of patients with cancer of the prostate. *Surg Gynecol Obstet* 1967, **124**, 1011–1017.
4. Bailar JC, Byar DP. Estrogen treatment for cancer of the prostate. Early results with 3 doses of diethylstilboestrol and placebo. *Cancer* 1970, **26**, 257–261.
5. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diath Haemorrhagica* 1965, **13**, 516–530.
6. Sagar S, Stamatakis JD, Thomas PD, Kakkar VV. Oral contraceptives, antithrombin III activity and postoperative deep-vein thrombosis. *Lancet* 1976, **6**, 509–511.
7. Blomback M, Edsmyr F, Kockum C, Paul C. Blood coagulation studies in patients with advanced carcinoma of the prostate treated with 2,6-*cis*-diphenylhexamethylcyclotetrasiloxane or estramustine-17-phosphate. *Urol Res* 1978, **6**, 95–102.
8. Blunt RJ, George AJ, Hurlow RA, Strachan CJL, Stuart J. Hyperviscosity and thombotic changes in idiopathic and secondary Raynaud's syndrome. *Br J Haematol* 1980, **45**, 651–658.
9. Kenny MW, George AJ, Stuart J. Platelet hyperactivity in sickle-cell disease: a consequence of hypersplenism. *J Clin Pathol* 1980, **33**, 622–625.
10. Buckell M. The effect of citrate on euglobulin methods of estimating fibrinolytic activity. *J Clin Pathol* 1958, **11**, 403–405.
11. Stuart J, George AJ, Davies AJ, Auckland A, Hurlow RA. Haematological stress syndrome in atherosclerosis. *J Clin Pathol* 1981, **34**, 464–467.
12. Laurell CB. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Ann Biochem* 1966, **15**, 45–52.

13. Clauss A. Gerinnungsphysiologische Schnellmethode zur bestimmung des Fibrinogens. *Acta Haematol* 1957, **17**, 237–246.
14. Roper JL, George AJ. A new lyophilized reagent for two-stage factor VIII:C assays. *Med Lab Sci* 1986, **43** (suppl), 35.
15. Varenhorst E, Wallentin L, Risberg B. The effects of orchidectomy, oestrogens and cyproterone acetate on the antithrombin III concentration in carcinoma of the prostate. *Urol Res* 1981, **9**, 25–28.
16. Agardh C, Nilsson-Ehle P, Lundgren R, Gustafson A. The influence of treatment with estrogens and estramustine phosphate on platelet aggregation and plasma lipoproteins in non-disseminated prostatic carcinoma. *J Urol* 1984, **132**, 1021–1024.
17. Rader ES. Hematologic screening tests in patients with operative prostatic disease. *Urology* 1978, **11**, 243–246.
18. Hendriksson P, Edhag O. Orchidectomy versus oestrogen for prostatic cancer: cardiovascular effects. *Br Med J* 1986, **293**, 413–415.
19. Varenhorst E, Svensson M, Hjertberg H, Malmqvist E. Antithrombin III concentrations, thrombosis and treatment with luteinising hormone releasing hormone agonists in prostate cancer. *Br Med J* 1986, **292**, 935–936.