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SEQUENTIAL AROMATASE INHIBITION AND ADRENAL BLOCKADE WITH AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER.

Robin Murray and Paula Pitt.
Cancer Institute. Melbourne, Australia.

It is uncertain whether the efficacy of aminoglutethimide (A/G) in advanced breast cancer (B/C) is due solely to its action in inhibiting peripheral aromatase activity or a combination of this with inhibition of adrenal androgen synthesis.
To answer this question 135 post menopausal women (median age 65 years range 37-90) with actively progressing advanced B/C were treated by aromatase inhibition with low dose (LD) A/G (125mg bd) without steroid supplements. On failure of initial treatment 65 of these women were changed to conventional dose (CD) A/G (250mg bd or tds) and steroid replacement (cortisone acetate 37.5mg/day ± Fludrocortisone 0.1mg/day), while 6 patients were continued on LD A/G and had the same steroid replacement added. Classification of response was according to UICC criteria. Thirty six (27%) of the initial 135 patients had an objective response to LD A/G and a further 12 (9%) had stabilization of disease. Eleven (17%) of the 65 patients changed to CD and steroids then had a response while arrest of the disease occurred in a further 5 (8%). Two of the 6 patients changed to LD and steroids also had an objective response. Tolerance to all regimes was excellent although two patients on LD developed signs of adrenal insufficiency.
Conclusions 1. Aromatase inhibition with LD A/G is an effective treatment in advanced B/C. 2. LD A/G and CD A/G and steroid replacement are not identical treatments as response to the latter may follow failure to the former. 3. It is likely that this difference is due to the addition of steroids rather than the increase in the dose of A/G.

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ADRENAL INHIBITION WITH TRILOSTANE IN ADVANCED BREAST CANCER.

Robin Murray and Paula Pitt.
Cancer Institute. Melbourne, Australia.

Adrenal inhibition with aminoglutethimide and physiological steroid replacement is now well established as a useful treatment for advanced breast cancer (B/C). The role of Trilostane (also an inhibitor of adrenal steroid synthesis) is less well defined. The aim of this study was to establish the therapeutic effectiveness and toxicity of Trilostane in patients with actively progressing B/C. To date 40 post menopausal or post oophorectomy women (median age 65 years range 37 - 82) have been treated with 960 mg/day of Trilostane and 37.5mg/day of cortisone acetate ± fludrocortisone 0.1mg/day. Classification of response was according to UICC criteria. Five patients were not eligible for assessment because of protocol violations and no decision has yet been reached in 3 patients. Of the remaining 32, twelve (37.5%) have had an objective response while a further 3 (9%) have had stabilization of previously progressing disease. Eight out of 17 patients (47%) who had previously responded to Tamoxifen and 2 out of 10 (20%) of non responders to Tamoxifen responded to subsequent Trilostane. Treatment was stopped in one patient who complained of feeling depressed and attempted suicide - she was subsequently found to have cerebral metastases. Other side effects (nausea in 6 cases, diarrhoea in 7 and tremoulousness in 1) either disappeared spontaneously or responded to simple medical procedures. Overall the drug was well tolerated. These results suggest that Trilostane is a useful second line agent in the treatment of advanced B/C.

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TRILOSTANE PLUS HYDROCORTISONE IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER. A PHASE II STUDY OF THE BELGIAN SOCIETY OF MEDICAL ONCOLOGY.

M. T'Hooft-Andry, C. Focan, A. Clarysse, J. Michel, J.C. Heuson and R. Paridaens (*).

Thirty three postmenopausal women with advanced breast cancer and measurable or evaluable lesions (UICC criteria) were treated with Trilostane (TRL) 960 mg/d, an adrenal blocking agent. The drug was combined with Hydrocortisone (HC) 40 mg/d, in order both to avoid Addisonian symptoms and to prevent a reflex rise in ACTH which would override a competitive Trilostane enzyme block. Most patients had far advanced disease, and had been heavily pretreated with hormones and chemotherapy. In eight cases the response could not be evaluated because of early death (3 pts), inadequate treatment (1 pt), loss to follow-up (1 pt), or premature drug withdrawal for intolerance (3 pts). Among the 25 fully evaluable cases, only 2 objective partial remissions were observed, which lasted for 10+ and 16 months. Response by dominant metastatic site was as follows : soft tissue 1 PR, 1 NC, 4 F; bone 1 PR, 4 NC, 6 F; viscera 3 NC, 5 F. Side-effects were recorded as mild to moderate in 6 cases, and as severe in 4 patients. They consisted of GI intolerance (6 pts), skin rashes (3 pts), and mineralocorticoid insufficiency corrected by Fludrocortisone (1 pt). Additional endocrine studies were carried out and results will be presented. Additional studies comparing TRL + HC to other endocrine modalities are required.

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(*) Correspondence to R. Paridaens, Institut J. Bordet, 1, rue Héger Bordet, Brussels, Belgium.

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INHIBITORS OF RAT TESTICULAR 17α HYDROXYLASE/C17-C20 LYASE

S.E. Barrie and A.B. Foster
Drug Development Section, Institute of Cancer Research, Sutton, Surrey, UK

Inhibition of androgen biosynthesis with the consequent reduction in the level of circulating androgens is one stratagem for the treatment of hormone dependent prostatic cancers. To achieve this selectively, inhibitors of the C17-C20 lyase step are being sought. The enzyme assay being used measures the 17α hydroxylation of ^{3}H-progesterone and the subsequent conversion of 17α-hydroxyprogesterone to androstenedione and testosterone by a microsomal preparation from rat testes (Brit. J. Cancer 52, 413, 1985). Several compounds showing activity in vivo against androgen dependent tissues were tested for inhibitory activity against the C_{17}-C_{20} lyase. Ketoconazole, an inhibitor of steroid biosynthesis, was potent in this test system (67% inhibition at 10μM). Flutamide, an antiandrogen, was ineffective (no inhibition at 100μM). Bifluoranol (erythro-3,3'-difluoro-4,4'-dihydroxy-α-methyl-α'-ethyl bibenzyl) showed intermediate activity (61% inhibition at 100μM). Several congeners of bifluoranol were also tested. The threo-analogue was less active (22% inhibition at 100μM). The des-fluoro- and the 3,3',5,5'-tetrafluoro- analogues were less effective (both 40% inhibition at 100μM). The α,α'-dimethyl and the α,α'-dipropyl analogues were also less active (15%, 45% inhibition respectively at 100μM) but the α,α'-diethyl analogue was more active (73% inhibition at 100μM. Bifluoranol is postulated to act at the pituitary but these results would indicate that direct inhibition of steroidogenesis at this step may also occur.