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PROGNOSTIC FACTORS FOR RESPONSE TO AMINOGLUTETHIMIDE IN BREAST CANCER

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145 metastatic breast cancer(MBC) patients(pts) were treated with Aminoglutethimide(AG)250 mg 4 times daily and hydrocortisone acetate 25 mg 2 times daily. A retrospective analysis on prognostic factors was performed in order to individuate features rendering pts likely to respond to AG.Main characteristics of pts were: median age 59 years(range 30-87);41 pts had been previously treated with adjuvant hormonotherapy and 62 pts with adjuvant chemotherapy;103 pts had been previously treated with tamoxifen(TAM)for MBC,of whom 19(16.7%) had responded to TAM. 27/109 pts experienced an objective response(OR)the actuarial 18 months progression free survival and overall survival are 13% and 46% respectively.The response rate observed in pts subsets are the following:pts postmenopausal > 5 years: 14/64(21.8%),pts postmenopausal from < 5 years:8/23(34.7%);pts oophorectomised: 5/22(22.7%); ER positive(> 10 fmol/mg)5/16 (31.2%);ER negative 5/20(25%); pts with disease free interval(DFI) after mastectomy > 24 months: 19/24(29.7%) pts with DFI < 24 months:8/45(17.8%); pts previously responders to TAM: 5/14(35.7%);pts previously non responders to TAM: 7/46(15.2%). In respect to site involvement OR were:bone(b)6/37, soft tissue(st)5/28, viscera (v)1/6; b + st 9/20; b + v 1/5; v + v + st 3/6.

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STRUCTURAL REQUIREMENTS OF INHIBITORS OF AROMATASE BASED ON AMINOGLUTETHIMIDE AND 3-PHENYLPYRROLIDINE-2,5,-DIONE.

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We have found' that 3-alkyl substituted 3-(4'-aminophenyl) pyrrolidine-2,5-diones (II) and aminoglutethimide (I;3-(4'-aminophenyl)-3-ethylpiperidine-2,6-dione) are equipotent as aromatase inhibitors. (I) has been successfully used in the treatment of oestrogen-receptor positive breast cancer in post menopausal women[2]. Using molecular graphics, we have examined the conformations of (I), (II), the active 3-(4'-aminobenzyl)pyrrolidine-2,5-dione (III) and the inactive hydantoin and spiro derivatives of (II). The following structural requirements (at least) appear to be essential : (1) the aniline nitrogen must not be coplanar with the flat or near flat heterocyclic ring, (2) a torsion angle (C_2-C_3-C_1'-C_2') between the hetero and aromatic rings in the range -10 to +50°, (3) a narrow range of low energy content conformations within this range so that the 'active conformation' is relatively more populated. The benzyl derivative (III) agrees with (1) and (3) above and has a plane-plane (aromatic-hetero ring) angle of +40° and can be superimposed on the active compound II so that the imide and aniline nitrogens are equivalent and the benzylic CH_2 group is in the same position as the 3-alkyl group of (II). The inactive hydantoin derivative of (II) has a similar torsion angle to that of the active compound but can exist in a wide range of low energy content conformers whereas the spiro compound is fixed in a conformation of torsion angle +70°.

1. Daly, M J. et al., J.Med.Chem., in press
2. Santen, R J., et al., Breast Cancer Res. Treat., 2, 375 (1982).

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AMINOGLUTETHIMIDE (AG) AND N-ACETYLAMINOGLUTETHIMIDE (AAG) INDUCE HEPATIC ENZYMES AND OESTROGEN METABOLISM IN THE RAT

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There are clinical reports that AG may induce hepatic enzymes. To unequivocally establish this activity, the inducing profile of AG and its metabolite AAG has been examined in Wistar rats. Animals received oral doses of either AG (60 mg/kg) or AAG (71 mg/kg) daily for 3 days. On day 4, various tests to detect hepatic enzyme induction were performed. Pretreatment with either compound reduced pentobarbitone hypnosis by 50%. There were significant ($P<0.05$) increases in liver weight and in hepatic microsomal protein and cytochrome P-450. There was also a 3-fold increase in the metabolism of pentobarbitone by the hepatic microsomes from pretreated rats. In addition, both AG and AAG caused significant increases in hepatic glucuronyl- and glutathione-transferase activity.

Pretreatment of immature female rats with AG or AAG significantly reduced the uterotropic activity of injected oestradiol (E) and enhanced the biotransformation of E to polar metabolites in these animals. Thus AG and AAG are enzyme inducers of the phenobarbitone type. The induction of E metabolism may represent an additional mechanism for the action of AG when used in breast cancer therapy. In like manner, the weak aromatase inhibitor AAG may also play a beneficial part in the therapy. If this proposal is correct, it would be useful to evaluate the incidence of breast cancer in post-menopausal women chronically receiving inducing agents e.g. antiepileptic drugs.

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DOES PRIOR PREDNISOLONE ADVERSELY AFFECT THE RESPONSE TO AMINOGLUTETHIMIDE?

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Aminoglutethimide and hydrocortisone is an effective endocrine treatment for post menopausal women with advanced breast cancer, producing an objective response rate of around 30% (range 16-43%, Stuart-Harris, Cancer Treat. Rev. 1984 11 : 189-204). The response is higher in women with oestrogen receptor positive (Er+ve) tumours and in those who have previously responded to endocrine therapy. We have studied the response in women given aminoglutethimide (1g daily) and hydrocortisone (40mg daily) (Ag+h) as second line treatment.

50 patients (pts) (median age 61 yrs, range 24-76) who received Ag+h for more than one month were studied. All had relapsed after Tamoxifen (10mg b.d.) with prednisolone (5mg b.d.) (37 pts) or ovarian irradiation with prednisolone (5mg b.d.) (13 pts) for advanced disease; chemotherapy had not been given, but 4 pts had received adjuvant chemotherapy. 30 pts had Er+ve tumours, in 20 the receptor status was unknown.

The overall objective response rate to Ag+h was 12% (CR:0, PR:6 pts) with a median duration of 11 months (range 4-20). 26 pts achieved stabilisation of disease (median 5 months, range 2-13). Only 3 of the 19 women who had an objective response to first line treatment showed a response to Ag+h. The response rate to Ag+h in heavily pretreated patients who have not received prednisolone in our unit is 29%, similar to that in previous reports (vide supra).

Our results suggest that prior exposure to prednisolone lowers the response to subsequent Ag+h and implies that the glucocorticoid given with conventional doses of aminoglutethimide is responsible for some of the anti tumour effect of the combination.