263 AMINOGLUTETHIMIDE (AG) COMBINED WITH PREDNISON (P) OR MEDROXYPROGESTERONE ACETATE (MPA) IN POSTMENOPAUSAL PATIENTS WITH ESTRADIOL RECEPTOR POSITIVE (ER+) OR ER-UNKNOWN ADVANCED BREAST CANCER REFRACTORY TO TREATMENT WITH TAMOXIFEN AND POLYCHEMOTHERAPY.

L.Beex, J.Raemaekers, G.Pieters, A.Koenders, A.Smals, Th.Benraad, P.Kloppenborg.
Dept. and Lab.of Endocrinology, University Hospital, Nijmegen, The Netherlands.

Thirty-three postmenopausal patients with ER+ (n=26) or ER-unknown (n=7) advanced breast cancer, refractory to treatment with tamoxifen and polychemotherapy, have been treated with AG(4x250mg orally daily) either combined with P (2x5 mg orally daily) and 9α-fluorohydrocortison (0,1 mg orally daily) or with MPA (500 mg i.m. daily for 4 weeks followed by 500 mg i.m. twice weekly).Objective remissions (according criteria of UICC) were achieved in 11 of 31 evaluable patients (35%) with a median duration of 7.5 (range 4-19) months. The estimated median survival times were 14.5 and 7 months ($p<0.01$) for patients responding or failing to therapy. Results in AG-P and AG-MPA treated patients were about equal. Toxicity (ataxia, lethargy, rash) although severe in 5 patients, was transient in all but 1 patient. Further side effects were overt hypothyroidism (n=2), Cushingoid symptoms (n=6) and weight gain (n=6) and were in all but 2 patients related with AG-MPA therapy ($p<0.05$). Endogenous adrenal cortical activity measured in terms of plasma ACTH and cortisol levels was more suppressed in the AG-MPA group than in AG-P treated patients. It is concluded that AG-P and AG-MPA are both effective treatment modalities for postmenopausal patients with ER+ advanced breast cancer, resistant to prior conventional polychemotherapy and tamoxifen. Cushingoid side effects and weight gain were most frequent in patients on AG-MPA therapy.

264 AMINOGLUTETHIMIDE WITHOUT CORTISOL SUBSTITUTION IN THE TREATMENT OF ADVANCED METASTATIC BREAST CANCER

B. Miller, A. Miller, R. Callies, and K. Höffken. Dept. of Gynecology and Dept. of Internal Medicine (Tumor Research), University of Essen, 4300 Essen, F.R.G.

Experiences in 16 postmenopausal patients suffering from metastatic breast cancer are presented. All patients had progressive disease under previous hormonal and/or chemotherapeutic regimens. Aminoglutethimid (AG) was administered in a dosage of 250 mg p.o. QID. No corticosteroids were given.

Serum levels of cortisol, dehydroepiandrosteronesulfate (DHEAS), TSH, T3, and T4 were determined at least weekly during the first month and monthly thereafter. Cortisol levels did not decrease significantly (Wilcoxon test), nor did DHEAS levels. TSH and thyroid hormones remained unchanged. AG had no influence on the levels of LH, FSH, prolactin, estradiol, and progesteron.

Patients were followed for 6 to 24 weeks so far. Partial response was observed in 1 patient (20+ weeks), stable disease in 7 patients (median 8+ weeks), and progressive disease in 7 patients. Side effects consisting of lethargy (8 pat.), ataxia (4 pat.), and skin rash (3 pat.) were moderate and disappeared after 2 to 4 weeks. In 1 elderly patient, treatment had to be discontinued because of mental confusion.

There is evidence that AG can be administered safely without cortisol substitution. It is still too early to evaluate long term side effects and therapeutic efficacy.

265 ENDOCRINE EFFECTS OF LOW DOSE AMINOGLUTETHIMIDE WITHOUT HYDROCORTISONE IN BREAST CANCER PATIENTS.

R. Stuart-Harris, M. Dowsett*, A. D'Souza*, S.L. Jeffcoate*, I.E. Smith. Breast Unit, Royal Marsden Hospital, London; *Endocrine Dept., Chelsea Hospital for Women, London.

Aminoglutethimide (AG) in combination with hydrocortisone (HC) suppresses plasma oestrogen levels in advanced postmenopausal breast cancer patients and is an active agent in their treatment. Oestrogen suppression has been thought to result from the inhibition by AG of the conversion of cholesterol to pregnenolone (adrenal desmolase) and androgens to oestrogens (peripheral aromatase). The conventional dose of AG was designed to achieve a "medical adrenalectomy" but the finding that AG is 10 times more potent in vitro on aromatase than on desmolase suggests that lower doses of AG may be effective in oestrogen suppression. We have studied the endocrine effects of low dose AG and conventional dose AG with HC in 33 patients with breast cancer. Initial dose of AG was 62.5 mg b.d.; dose was doubled at monthly intervals until patients had received AG 500 mg b.d. for one month, when HC 20 mg b.d. was also added. Significant suppression of serum oestrone and oestradiol values occurred at the lowest dose of AG compared with pretreatment values ($p < 0.001$). Further significant suppression of oestrone ($p < 0.05$), but not oestradiol occurred at 125 mg b.d. No further suppression of oestrone or oestradiol occurred at higher doses of AG or on the addition of HC. 125 mg AG b.d. is as effective in suppression of oestrogen levels as conventional doses, and should be assessed for clinical effectiveness.