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ENDOCRINE ASPECTS AND HORMONAL TREATMENT OF HEPATOCELLULAR CARCINOMA: AN OVERVIEW

P.J. Johnson
Liver Unit, King's College Hospital, Denmark Hill, London SE5 8RX.

Several clinical observations suggest that hepatocellular carcinoma (HCC or "hepatoma") may be a hormone dependent tumour: the apparent relation to anabolic steroids and oral contraceptive preparations, and the striking male predominance particularly among patients with cirrhosis. In many animal models thyroid hormones, prolactin and testosterone stimulate tumour growth, and the latter may enhance the progression of chemically induced hyperplastic nodules to frank malignancy. In animals and humans, both oestrogen and androgen receptors have been reported in normal and malignant liver tissue though some of the evidence is conflicting and the amounts detected vary widely. From a therapeutic standpoint, we failed to show any advantage from the addition of tamoxifen to adriamycin, in a controlled trial although other workers have,more recently, reported prolonged survival using tamoxifen alone. About 20% of HCC patients receiving the anti-androgen cyproterone acetate showed a clinical response.

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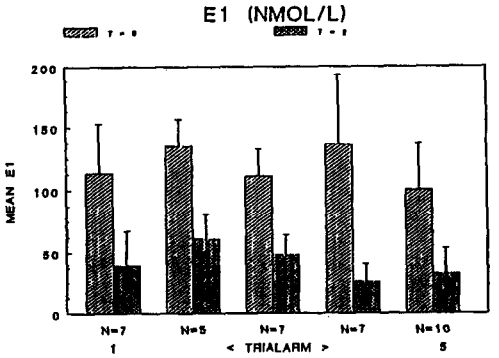
Second-line endocrine treatment of postmenopausal metastatic breast cancer: a 5-arm randomized trial (EORTC 10852).

P.F.Bruning (The Netherlands Cancer Institute, Amsterdam), on behalf of the EORTC Breast Cancer Cooperative Group.

The supposed mechanism of action of aminoglutethimide (AG), medical adrenalectomy, has been challenged and AG is now considered to act as an inhibitor of the aromatization of mainly adrenal androgens to estrogens in peripheral tissues and/or breast cancer itself. To further establish the AG dose required to sufficiently reduce estrogen levels in plasma, the possible role of hydrocortisone (HC) in combination with AG or by itself, postmenopausal advanced breast cancer patients received AG low (125 mg b.d.) or medium (250 mg b.d.) dose alone or combined with HC (20 mg b.d.) or HC alone (20 mg b.d.).
Preliminary data show a similar reduction of plasma estrone at 8 weeks by at least 60% in all treatment arms. Further results of this prospective randomized endocrine comparison will be discussed.



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EXPERIMENTAL COMPARATIVE STUDIES WITH THE NEW AROMATASE INHIBITORS CGS 16949 AND CGS 20267

A.S. Bhatnagar, A. Häusler, K. Schieweck, M. Lang & R. Bowman.
Research Departments, Pharmaceuticals Division, CIBA-GEIGY Ltd. Basel, Switzerland and CIBA-GEIGY Corp., Summit, NJ, USA

CGS 16949A is a non-steroidal aromatase inhibitor which has been profiled as a highly potent and efficacious inhibitor of estrogen biosynthesis in vitro and in vivo in adult female rats. Through its inhibition of aromatase, it has been shown to be effective in causing almost complete regression of DMBA-induced mammary tumors when administered orally to female rats. In healthy male volunteers and postmenopausal women with breast cancer it potently and dose-dependently reduces circulating estrogens. However, at high concentrations and doses in vitro and in vivo, it inhibits the biosynthesis of aldosterone.
CGS 20267 [4,4'-(1H-1,2,4-triazol-1-ylmethylene)-bis-benzonitrile] is a new non-steroidal aromatase inhibitor which has not been described previously. In vitro it is as potent as CGS 16949A but in vivo it is about 10-30 times more potent in the inhibition of androstenedione-induced uterine hypertrophy assay for aromatase. In terms of selectivity, CGS 20267 is even more selective in its inhibition of aromatase than CGS 16949A in that it only inhibits aldosterone production in vitro at concentrations which are 6000 times higher than those required for inhibition of estrogen production. In vivo, CGS 20267 does not suppress either corticosterone or aldosterone at doses which are over 500 times higher than the ED_{50} for aromatase inhibition in vivo.
In adult female rats, at a maximally effective oral dose of 1 mg/kg administered once daily over 14 days, CGS 20267 reduces uterine weight and increases circulating LH to those seen 14 days after surgical ovariectomy. When administered to adult female rats bearing DMBA-induced mammary tumors, CGS 20267 was as effective at causing the regression of existing tumors and suppressing the appearance of new tumors as surgical castration. This anti-tumor efficacy was accompanied by the endocrine sequelae of castration. Thus at its maximally effective oral dose, CGS 20267 elicits endocrine effects and anti-tumor efficacy which are equipotent with those seen after castration.

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RECENT PROGRESS IN DEVELOPMENT OF AROMATASE INHIBITORS

Richard J. Santen
The Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA

In postmenopausal women with breast cancer, aromatase, which is the enzyme converting androstenedione to estrone and testosterone to estradiol, is the rate-limiting step in estrogen biosynthesis. The currently available aromatase inhibitor, aminoglutethimide, effectively blocks estrogen production and produces tumor regressions in patients previously treated with tamoxifen. This drug, however, produces frequent side effects and blocks steroidogenic steps other than the aromatase enzyme. Thus, newer aromatase inhibitors with greater potency and specificity are under intense study. More than 20 such compounds have recently been developed. In several clinical trials, 4-hydroxy-androstenedione, given parenterally, has been highly active and specific for aromatase inhibition in patients with breast cancer. In two large recent studies, one-third of heavily pretreated women experienced objective tumor regression with this therapy. CGS 16949A, a newer agent, is also in Phase III clinical trials. This compound is an imidazole derivative with nearly 1,000-fold greater potency than aminoglutethimide. An initial Phase I study compared the potency of 0.6 to 16 mg daily in 12 postmenopausal women and found maximal suppression of urinary and plasma estrogens with 2 mg daily. The degree of inhibition was similar to that induced by aminoglutethimide or by surgical adrenalectomy. No CNS, hematologic, or biochemical toxicity was observed. A larger Phase II study in 54 patients confirmed this high degree of potency of CGS since a plateau effect was observed at the 1.8, 2.0 and 4 mg daily doses. The endocrine effects were not absolutely specific as a blunting of ACTH-stimulated but no basal aldosterone levels were observed. This and other emerging aromatase inhibitors offer promise as pharmacologic methods to inhibit estrogen production specifically and without side effects.