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HORMONAL ASPECTS AND TREATMENT OF ENDOMETRIAL CARCINOMA

J.A. Wijnen,Dept.Gynaecological Oncology,Univ.Hosp."Dijkzigt" and The Dr.Daniel den Hoed Cancer Center, Rotterdam.

Since the early fifties numerous studies have confirmed the link between unopposed estrogen exposure and the increased risk of endometrial cancer and its precursors. The increasing incidence of endometrial carcinoma and a better understanding of prognostic factors have induced a growing interest in this disease in recent years. A multitude of treatment regimes has been reported. The overall 5-years survival rate as presented in the 1985 Annual Report of the F.I.G.o was 67.7%. Surgery is generally accepted as the cornerstone in the management of endometrial carcinoma and can cure more than half of all patients. Until now the additional treatment of choice is radiotherapy. Experience with chemotherapy in endometrial cancer patients is limited and restricted to advanced or recurrent disease.

Progestogens have a privileged position as a systemic therapy for endometrial cancer. Their popularity is due to the general ease of administration, good tolerance and reported objective response rates of 11-45% in patients with advanced or recurrent disease. The likelihood of response will be increased by features as better tumor differentiation,which appears to be related to higher degrees of progestogen - receptor binding in tumor tissue; a long disease-free interval; local pelvic recurrence and a single focus of disease. As with chemotherapy, in many cases responses on hormonal treatment have been of short duration. The benefit of adjuvant progestogen treatment in early stage endometrial cancer has not been established yet. The occasional dramatic clinical regression or prolonged stabilization occuring during progestogen therapy supports a continued but more limited and selective role for these agents.

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ALTERNATING AND COMBINED TREATMENT WITH TAMOXIFEN AND PROGESTINS IN POSTMENOPAUSAL BREAST CANCER.

J. Alexieva-Figusch,F.H. de Jong,S.W.J.Lamberts,A.Planting M.A. Blankenstein,J.Blonk-v.d.Wijst and J.G.M. Klijn. Dept.of Int.Med.and Clin.Endocrinol.Dr Daniel den Hoed Cancer Center and Erasmus University,Rotterdam,The Netherlands.

Antiestrogens and progestins are extensively used in breast cancer treatment. In a retrospective study in unselected patients we found no difference in response rate (CR+PR)and its duration between tamoxifen (TAM) and megestrol acetate (MA) as first line treatment.Because of different effects on hormone secretion and steroid receptor synthesis,the question arises whether combined or alternating treatment could cause better results than single treatment. In 3 consecutive studies the endocrine effects during single (MA), combined (TAM+MA)and alternating (TAM and MPA)treatment were: Single treatment with MA (n=18): the main endocrine effects are suppression of the pituitary-gonadal and -adrenal axis and stimulation of prolactin (PRL). Combination treatment (n=6): the addition of TAM to MA caused abolishment of the stimulating effect of MA on PRL secretion, more pronounced suppression of gonadotropins and estradiol (E_2),while cortisol remained unchanged in comparison to the results during single MA treatment. Alternating treatment (n=26) (1 week TAM followed by 3 weeks of MPA) caused no effect on PRL, but strong suppression of gonadotropin secretion,while plasma E_2 decreased with 40% in comparison to 22% during single MA treatment. The adrenal suppression by MPA appeared partly reversible during 1 week treatment with TAM. However,on the basis of endocrine and side-effects,MPA appeared the dominant agent of the alternating therapy. Clinical effects in this selected group (ER+ or DFS > 2 year):50% CR+PR (15+months) and 34% stable disease (7+months).Longer follow-up and randomised studies are needed to show whether this alternating hormonal treatment is of additional value.

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PROLACTIN RECEPTORS IN BREAST CANCER

M. L'Hermite-Balériaux, S. Casteels and M. L'Hermite. Université Libre de Bruxelles, Dept. of Gynaecology and Obstetrics, Hôpital Brugmann, Bruxelles, Belgium.

The occurrence of prolactin-receptors (Prl-R) in human breast tumours has presently been firmly established. We investigated 199 breast tumours, using three different techniques for membrane preparation, according to, respectively, Shiu, Bonneterre and Martin. A tumour was considered to be positive when the difference between the specific binding (Sp B) and the non-specific binding (N Sp B), in presence of 1 mcg O Prl, was greater than 0.8 %. O Prl was used for labeling. The overall rate of positive tumours is 19 %; it varied, however, considerably according to the type of preparation of the membranes used for detection of Prl-R : 14.5 % (Martin), 24 % (Bonneterre) and 34 % (Shiu). The significance of this variation should be further investigated. In 164 of these cases, for which ER and Pg-R were available, no correlation could be evidenced between steroid-receptors and Prl-R : Prl-R positive tumours could exhibit either positive or negative steroid-receptors. The clinical implications of the presence of Prl-R still remains to be established.

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PROLACTIN AND BREAST CANCER

P.F. Bruning
The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), Amsterdam, The Netherlands.

One of the many different biological actions of prolactin (PRL) is to promote mammary tumors, both spontaneous and induced, in rat and mouse. The role of what has been measured as PRL in the pathogenesis of human breast cancer is still uncertain. Elevated immunoreactive plasma PRL is not unequivocally related to manifest breast cancer or to increased risk because of a strongly positive family history or the occurrence of benign breast disease. Geographical patterns of breast cancer distribution could not be explained by observed plasma PRL. First full-term pregnancy which, when at young age, protects from breast cancer is followed by a long-lasting decrease of plasma PRL. However, pregnancy itself means exposure to high PRL levels. No consistent evidence is available showing that prolonged exposure to drugs increasing plasma PRL entails an increased breast cancer risk. Oral contraceptives which may raise PRL have been reported to protect from benign breast disease. However, young women using the pill before first pregnancy may have an elevated risk of breast cancer. Human PRL research has been made difficult by considerable fluctuations of plasma levels due to circadian rhythm, stress, etc. and by the long interval needed for a hormone to exert its influence on the eventual manifestation of cancer. More recently, demonstration in normal human plasma of various molecular PRL moieties with very different bioactivity has raised the possibility that cleaved PRL may be of greater interest than the classical 198 aminoacid PRL.