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LHRH AGONIST TREATMENT OF BREAST CANCER: A PHASE II STUDY IN THE U.S.A.

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The Abbott Study Group in the U.S.A. has undertaken multi-center trials of Leuprolide (D-Leu^{6} GnRH) in women with metastatic breast cancer. In 25 premenopausal patients, Leuprolide in a dose of 1 mg. s.c. daily produced an objective response rate in 11 (44%) patients and disease stabilization in 5 (20%). The median duration of response was 39 weeks. Responses were seen in 4 of 10 ER neg. and in 6 of 11 ER positive tumors. This GnRH analog caused complete chemical castration as evidenced by amenorrhea, and levels of estrone, estradial and progesterone in the postmenopausal range. Higher doses of leuprolide (5 and 10 mg) did not produce any greater effects. Toxicity was minimal and there was no significant tumor flare. In earlier studies of 41 postmenopausal patients similarly treated with leuprolide, the combined objective response rate was less than 10%. We conclude that leuprolide is a safe and effective means of treating metastatic breast cancer in premenopausal women. The predominant mechanism of action is through ovarian suppression of estrogen production, an effect consistently achieved when this analog is administered by daily s.c. injection. Further studies comparing leuprolide to oophorectomy and tamoxifen ± leuprolide are being planned.

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BRITISH EXPERIENCE WITH THE LH-RH AGONIST ZOLADEX IN BREAST CANCER. R.I. Nicholson, Tenovus Institute for Cancer Research, Cardiff, U.K.

The effect of either daily injections (500-1000µg/day) or a sustained release formulation (3.6 mg/month) of Zoladex (ICI 118630, D-Ser(Bu^{t})^{6}Azgly^{10}-LH-RH) on pituitary gland and ovarian function has been investigated in 80 patients with advanced breast cancer. In pre and postmenopausal women both formulations of Zoladex produced an initial rise in circulating concentrations of gonadotrophins. However, on continued treatment (>14 days) plasma LH and FSH levels decreased to below pre-treatment values. This was especially evident for LH. In premenopausal patients plasma progesterone and oestradiol levels were significantly reduced after 1 month of therapy, reaching values observed in oophorectomised women. No substantial acute or long-term influence of Zoladex on these hormones was seen in postmenopausal patients. Breast tumour remissions were recorded in 14/45 (31%) premenopausal women and in 2/9 postmenopausal patients. Clinical responses were observed only in women with ER positive (12/21) or ER unknown (4/8) disease. Oophorectomy after disease progression was performed on 24/45 premenopausal patients. Of 22 women who failed to respond to Zoladex, 18 subsequently failed to respond to oophorectomy. No response to oophorectomy was observed in two women who previously responded to Zoladex.

Experimental studies designed to detect direct inhibitory actions of Zoladex on oestrogen sensitive tissues of the rat and on carcinogen-induced mammary tumours proved negative. Indeed, implantation of the sustained -release formulation of Zoladex directly into this tumour type produced no evidence for either localised inhibitory actions of the drug or additional benefit in terms of rate of tumour regression. The clinical ramifications of these data will be discussed.

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LONG-TERM LHRH-AGONIST (BUSERELIN) TREATMENT IN METASTATIC PREMENOPAUSAL BREAST CANCER.

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In 1982 we reported for the first time (Lancet 1:1213-1216, 1982) that chronic LHRH-agonist (Buserelin) treatment can cause objective tumor regression in premenopausal pts. with metastatic breast cancer in the presence of medical castration. Between 1981 and jan.1985 we have treated 32 pts. with now a minimal follow up of 1.5 year. They were treated intranasally (i.n.) and subcutaneously (s.c.) with different dosages of Buserelin (2x1.0 mg s.c.-3x0.4 mg i.n.) during 3-54 months. Nine pts. were treated in combination with tamoxifen or megestrol acetate from the start of therapy. The updated results show that in the whole group 14 pts.(44%) showed objective remission (x=19^{+}m, range 3-54^{+}m), 6(19%) stable and 12(37%) progressive disease. An objective response during single Buserelin treatment was found in 9 out of 23 pts.(39%) and in 45% of pts. with ER-positive tumors. Eight pts.(25%) died within 1.5 year after start of treatment; 13 out of 24 pts.(54%) with a follow up of at least 3 year survived longer than 3 year. The occurrence of complete medical castration and the suppression of gonadotropin secretion appeared dose dependent.One patient showed tumor recurrence after escape of complete ovarian function suppression during gradual dose decrement (2.0 to 0.8 mg/day) followed by a second complete remission after reinstitution of medical castration by dose increment of the LHRH-agonist. I a recent review of the literature we calculated an objective response rate in 38%(44/116) of premenopausal and in 11%(12/109) of postmenopausal pts. In conclusion: chronic LHRH-agonist treatment appears as effective as other common kinds of endocrine treatment in premenopausal breast cancer in the absence of serious side effects. For a complete medical castration in all pts. a daily dose of at least 1 mg s.c. is needed.

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LHRH AGONIST TREATMENT IN OVARIAN CANCER

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Experimental animal observations and human epidemiological and receptor studies suggest that many ovarian tumours are endocrine-related. An inhibitory effect through the suppression of pituitary FSH and LH secretion by administration of GnRH superagonist has recently been suggested. This has now been further tested both in an animal model and in a pilot study as second-line therapy in women with advanced ovarian cancers. Two groups of 4-week old female R-rats were castrated and one ovary was at the same time autotransplanted intrasplenically. One year after the operationwhen the animals had developed ovarian tumours in the grafts, one group (n = 9) started to receive daily subcutaneous injections of 25 ug of GnRH superagonist. D-Trp-6-LH-RH, while the control group (n = 7) received sham injections. The tumour growth was monitored by repeated laparotomies. In controls the tumours grew rapidly while suppression of growth soon occurred, with the tumours remaining practically static for a year, in GnRH superagonist treated rats.

In 10 women agonist treatment was started after failing cytostatic regime had been abandoned for one month. 100 ug/day sc initially for 7 days and subsequently monthly injections of a slow-release preparation of D-Trp-6-LHRH microcapsules designed to release 100 ug/day was given. Basal levels of gonadotropins were suppressed. Tumour shrinkage or static tumours was observed in 5 cases with clinical remission for 4-6 months. The survival under the agonist treatment, 1-24 months, seemed to be free of haematological or chemical side effects. The benefits of this simple and non-toxic treatment included, beside tumour remission, in some cases also diminishing ascites and recovery of bone marrow activity.