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A PHASE II TRIAL WITH D-Trp-6 (DECAPEPTYL) IN PREMENOPAUSAL RH+, HORMONAL UNTREATED ADVANCED BREAST CANCER PATIENTS.

E.Garcia-Giralt, P.Beuzeboc, T.Dorval, M.Jouve, A.Livartowski, T.Palangie, S.Scholl, P.Pouillart.
Institut Curie, Dpt Médecine Oncologique.
Paris, France.

LHRH analogues are suitable first-line agents for the treatment of premenopausal breast cancer patients because their efficacy is comparable with that of surgical castration and because they lack serious side effects. D-Trp-6 is a analogue of LHRH which inhibits breast cancer cell growth by several direct and indirect mechanisms. In a trial including 20 patients treated with s.c. injection of 3.75mg (each 28th day) of 6-Trp-6 for 3 to 35 months, no important side effects occured with the exception of those caused by the intended hypogonadism, expecially hot flushes. A few patients had more or less short-term urticarial skin irritation wich did not cause pain or disconfort. Of 19 evaluable patients there were 4 CR (>4, 20, 23, and 35 months), 8 PR, 1 stable disease and 6 patients progressed.
We concluded that D-Trp-6 is a non toxic and clinically active inhibitor of breast tumor proliferation in premenopausal RH + selected patients.

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Gn-RH ANALOGUE GOSERELIN (ZOLADEX) IN THE TREATMENT OF PRE-AND PERIMENOPAUSAL WOMEN WITH METASTATIC BREAST CANCER RESULTS OF A MULTICENTRIC STUDY.

A.R.Bianco(1), S. De Placido(1), F.Calabresi(2), M.Fiorentino(3), V.Fosser(4), R.Lenti(5), R.Rosso(6), P.G. Simondi(7), R. Artioli(8), ITALY.
1)Division of Medical Oncology, University of Naples Medical School II; 2)Division of Medical Oncology, Tumour Institute, Regina Elena, Rome; 3)Division of Medical Oncology, General Hospital of Padua; 4)Division of Medical Oncology, General Hospital of Vicenza ; 5)Division of Nuclear Medicine and Oncology, General Hospital of Teramo; 6)Division of Medical Oncology, Tumour Institute, Genoa; 7)Division of Obstetrics and Gynaecology, University of Turin; 8)ICI Pharma; ITALY.

Sixty-four pre-perimenopausal patients with metastatic breast cancer (mean age 42 years, range 28-56) were subjected to 'Zoladex', a long acting GnRH-analogue depot preparation, injected s.c. every 28 days. 53 patients were evaluable, of whom 24 had received adjuvant cytotoxic chemotherapy, 2 adjuvant hormonotherapy and 27 no previous treatment. Dominant site of metastases was soft-tissue(loco-regional) in 14, bone in 16 and visceral in 23. Serum oestradiol, LH and FSH were suppressed by 'Zoladex'. Mean oestradiol values fell into the range of castration values within 4 weeks of therapy and this suppression was maintained throughout therapy. 16/53 (30.2%) patients showed an objective response: 5(9.4%) a complete response and 11(20.7%) a partial response. Median duration of response was 36 weeks (range 16-76). Site of response was loco-regional in 64%, bone in 12%, and viscera in 22%. Objective response according to menopausal status was obtained in 15/46(32.6%) in premenopausal and 1/7(14.3%) in perimenopausal patients. Zoladex was administered easily s.c. each month and was well tolerated without serious toxicity. No patient was withdrawn due to an adverse reaction.

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GROWTH INHIBITORY EFFECT OF SOMATOSTATIN ANALOG (RC-160) IN MCF-7 CELLS.

M.A. Llorens, A.L. Charro and M. Puente.
Hospital Universitario San Carlos, Servicio de Endocrinología, Metabolismo y Nutrición, Madrid, Spain.

Various hormones and growth factors have been implicated in the growth regulation of human breast cancer. Breast cancer cells have been shown to produce IGF-1 and EGF polipeptides with confirmed mitogenic activity and autocrine growth factor properties. Somatostatin and its analogs either directly or indirectly through suppresion of growth hormone, can inhibit the action of these growth factors. To confirm the direct paracrine or autocrine inhibitory actions of somatostatin in cell proliferation we have studied a new somatostatin analog (RC-160) for the ability to inhibit the growth of MCF-7 cells.
Cells (5.10^4) were either cultured in 24-wells clusters in medium supplemented with 10% inactivated and steroid depleted fetal calf serum or in 10% fetal calf serum that had been inactivated for 30 min. at 56ºC (complete growth medium, CGM). Cells were plated at densities indicated above and the following day somatostatin analog (0.01nM to 1µM) or control vehicle were added to the wells. One, three and five days later cells were harvested and counted in an hematocyter. DNA content of the cells was estimated by a fluorimetric method. Proliferation of cell cultures in CGM medium was significantly inhibited (40%-70%) at 10nM concentration of RC-160. DNA content of cell cultures showed growth decreases at various somatostatin analog concentrations and maximal decrease (60%) was again observed at 10nM of RC-160. Growth inhibition was less pronunced when steroid depleted serum was used in the medium. In this case maximal decrease (50% of controls) in cell number have been obtained at concentrations of somatostatin analog 10nM. Similar results were obtained when DNA content of cells was analyzed.
We conclude that somatostatin analog (RC-160) has a direct inhibitory effect on proliferation of MCF-7 cells.

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THE ENDOCRINE EFFECTS OF BROMOCRIPTINE AND SMS 201-995 IN ADVANCED BREAST CANCER PATIENTS

E Anderson, H Morten, [1]J Ferguson, [2]SM Shalet, [3]L Robinson and [1]A Howell, Dept's of Clinical Research, [1]Medical Oncology, [2]Endocrinology & [3]Chemical Pathology, Christie & Withington Hospitals, Manchester, UK.

Six patients who had failed first and second line endocrine therapies received bromocriptine (2.5mg bd, po) and SMS 201-995 via a continuous subcutaneous infusion (200 or 400ug/24h) until disease progression. At the start of treatment 24h profiles of serum lactogenic hormones were established. These profiles were repeated at 2 wks, 3mths and 6mths (or at tumour progression) after the start of treatment. Immunoreactive prolactin and growth hormone (ir-PRL and ir-GH) were measured by RIA, bioactive lactogen (BL) was estimated using the Nb2 rat lymphoma cell bioassay. Before treatment all pts showed episodic secretion of ir-PRL, ir-GH and BL. After 2 weeks of treatment, ir-PRL was reduced to below the limit of detection, peaks of ir-GH were still apparent and correlated well with the BL levels. In one patient who was profiled at 3 and 6 months after the start of treatment, ir-PRL remained suppressed and episodic secretion of ir-GH and BL was still evident. Of the six pts treated, two showed stabilisation of their disease. These results indicate that ir-PRL can be effectively suppressed in advanced breast cancer patients but SMS 201-995 at the doses used does not completely abolish ir-GH secretion.