III - j

COMPARATIVE STUDIES WITH LHRH-AGONISTS

H.J. de Voogt
Dept of Urology, Free University Hospital, Amsterdam, the Netherlands

At present the number of studies comparing LHRH-agonists with standard anti-androgenic therapy is very small.
We could find only five reported sofar. Of these the study of Garnick et al. has the largest number of patients (199) and can be regarded as a real randomized prospective phase-III-study, with a two-year follow-up.
The other studies use ranges of 25-80 patients. Follow-up periods ranged from 3-18 months.
The drugs used were leuprolide and Buserelin, in daily doses or as longacting preparations. Comparison was with orchiectomy, DES or an anti-androgen.
A favourable response was seen in between 65-85% of all treatment groups and similarly the fall of serum-T-levels and (P)AP-levels was the same.
Patients treated with DES had the expected rate of cardiovascular side-effects. In the patients treated with LHRH-agonists no other side-effects than hot flushes were noted.

The overall conclusion is that at present there is no difference in treatment-effect between patients with advanced PCA, treated with LHRH-agonists or with standard anti-androgenic treatment.

Long-term follow-up with LHRH-a,yes or no combined with anti-androgens,will be necessary to determine whether such a difference eventually will show. To this end the EORTC Genito-urinary group has embarked on 2 studies, comparing LHRH-agonists with orchidectomy and the combination of LHRH-a + anti-androgens. Simular studies are underway in the U.S.A.

III - k

LEUPROLIDE (LEU) VS. DIETHYLSTILBESTROL (DES) FOR PREVIOUSLY UNTREATED STAGE D2 PROSTATE CANCER

Marc B. Garnick, M.D. for the Leuprolide Study Group
Dana-Farber Cancer Institute, Boston, MA 02115

Gonadotrophin releasing hormone analogues have recently shown therapeutic efficacy in the management of patients (pts) with metastatic prostate cancer. The current, prospectively randomized trial was undertaken to compare the efficacy and safety of LEU (1 mg subcutaneously daily) to DES (3 mg p.o. daily) in previously untreated, stage D2 prostate cancer pts. Initial therapy (LEU or DES) continued for as long as an objective response was noted; crossover to the alternate arm occurred at time of disease progression or intolerable adverse reactions. Criteria of the NPCP were used, and all pts were required to have at least two measurable/evaluable indicator lesions for response. Ninety-eight pts were randomized to LEU; 101 pts to DES. The distribution of age, performance status, and prostatic acid phosphatase were comparable between groups. Approximately 80% in each group had multiple bone lesions and/or visceral metastases. Suppression of testosterone, dihydrotestosterone, and decrease in acid phosphatase were comparable between groups. Pts assigned to DES experienced more painful gynecomastia ($p < .00001$), nausea and vomiting ($p = .02$), edema ($p = .008$), and thrombotic/embolic phenomena ($p = .065$) compared to LEU assigned pts. LEU pts experienced more "hot flashes" ($p = .00001$). Overall, 86% of LEU pts demonstrated an objective response [complete response (CR) - 1%; partial response (PR)-37%; stable disease (SD) - 48%] compared to DES pts (CR - 2%; PR-44%; SD-39%). Actual survival rates at one year are 87% for LEU pts and 78% for DES pts ($p = .17$) (Fisher's exact test). We conclude that LEU offers an important alternative treatment which is therapeutically equivalent and potentially less deleterious than DES for the initial management of pts with metastatic prostate cancer.

III - l

PHASE II TRIAL OF D-Trp-6-LH-RH (LONG RELEASING FORMULATION) IN ADVANCED PROSTATIC CANCER.

G. Mathé, R. Kelling, G. Prévot, M.L. VoVan, J. Gastiaburu, G. Prévot, J.M. Vannetzel, R. Despax, C. Jasmin, F. Lévi, M. Musset, D. Machover, P. Ribaud and J.L. Misset. SMST & ICIG (Univ. Paris-Sud, CNRS UA 04-1163, Assoc. CI-Bernard & ARC), Hôpital Paul-Brousse, 94804 Villejuif, France.

39 patients (pts) with histologically confirmed prostate cancer have been treated with sustained release formulation of D-Trp-6-LH-RH (SRF). The pts received a daily s.c. injection of 500mcg of immediate formulation D-Trp-6-LH-RH (IF) followed by an IM injection every 28 days of SRF, releasing daily 100mcg. Median age was 70 years (58-83). Thirty one/38 pts were heavily pretreated. Thirty six pts (32 stage D, 2 stage C and 2 stage B) are evaluable after 3 months therapy; 3 pts are not evaluable because of protocol violations; 6 had progressive disease. SRF induced a marked decrease in LH and testosterone levels. Antitumor action was evaluated on: a) subjective manifestations: urinary symptoms, which improved in 15/24 pts (62%) and bone pain in 11/16 pts (69%), b) objective measurements: prostatic size evaluated by transabdominal ultrasonography was normalized or reduced in ≥ 50% in 3/12 (25%) and by ≤ 50% in 5/12 pts (41%). Prostatic acid phosphatase regressed to normal in 2/8 pts and to ≥ 50% in 2/8 pts. Bone scan showed a marked improvement in 3/18 (16%) pts. Six pts progressed under treatment. In a previous study of (IF) D-Trp-6-LH-RH the median duration of response in responders was slighly inferior to one year. We conclude that the D-Trp-6-LH-RH (SRF) is as active as the IF showed to be in a previous study. Therefore we recommend SRF D-Trp-6-LH-RH in order to improve local tolerance, acceptance and continuity of the treatment.

III - m

PHASE II TRIAL OF D-Trp-6-LH-RH IN ADVANCED BREAST CANCER

G. Mathé, R. Kelling, M.L. VoVan, J. Gastiaburu, G. Prévot, J.M. Vannetzel, R. Despax, C. Jasmin, F. Lévi, M. Musset, D. Machover and J.L. Misset.
SMST & ICIG (Univ. Paris-Sud, CNRS UA 04-1163, Assoc. CI.-Bernard & ARC), Hôpital Paul-Brousse, 94804-Villejuif, France.

A total of 23 patients (pts) with advanced breast carcinoma were treated with an LH-RH analogue, D-Trp-6-LH-RH (Debiopharm, Lausanne) with a starting dose of 500mcg s.c. for 7 days, followed by either daily s.c. injection of 100mcg (12 pts) or one monthly i.m. injection (11 pts) of its sustained release formulation. Eight pts had local therapy and 15 pts were previously treated with hormonal and/or chemical therapy. Age ranged from 35 to 85 years. Decrease levels of LH were efficiently obtained with both schedules. Eight pts were premenopausal (PM) and 15 postmenopausal (PMP); 5/8 PM pts were ER+, 3 of whom were responders (2CR+1PR); ER were unknown in the remaining three pts, none of whom responded; 3/15 PMP pts were also responders; 2 of these pts were ER+ (1CR+1PR). We conclude that sustained release formulation (SRF) D-Trp-6-LH-RH is as efficient as the immediate formulation one (IF) to obtain LH decrease levels. SRF D-Trp-6-LH-RH was better tolerated locally. Both D-Trp-6-LH-RH showed antitumoral activity in advanced breast cancer heavily pretreated. These data suggest that D-Trp-6-LH-RH is preferentially active in ER+ pts, and also that it may have a direct antitumoral action, independent of that of the hypothalamic-hypophysial gonadal axis.