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ENDOCRINOLOGICAL ASPECTS OF LH-RH DEPOT-PREPARATION (ICI 118.630) IN ADVANCED PROSTATIC CANCER.

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In the treatment of advanced prostatic cancer, various endocrine therapies have been used, all of them leading to a decrease of serum testosterone (T) levels and thus preventing the stimulation of androgen-dependent growth of prostatic tumors. However, the side-effects of the conventional therapies are rather severe. Superactive LH-RH analogs efficiently suppress the gonadal T-production without significant side-effects. In a group of 70 patients with advanced prostatic cancer, that were treated with a relatively low dosage of LH-RH analog(The first depot preparation, Zoladex 3.6 mg every 4 weeks), T and dihydrotestosterone (DHT) levels decreased, after an initial rise at 3-5 days, within 4 weeks to levels observed in orchidectomized patients. LH and FSH levels also decreased substantially. To eliminate the initial androgen rise, diethylstilbestrol (DES) was administered (1mg daily) to 13 patients from 1 week prior to 4 weeks after the first LH-RH administration. This treatment however, could not prevent the initial rise of T and DHT. The concentration of 17-α-OH-progesterone (17OHP) was measured in 5 patients and peaked at day 2 after start of therapy, but then rapidly decreased to levels of approximately 25% of the initial value. The response of LH on LH-RH (100µg i.v.) established in 5 patients was virtually abolished between 7 and 10 days from the beginning of the treatment. Conclusions: 1. This LH-RH depot efficiently reduces serum androgen leves, 2. The pituitary gland is apparently desensitized, 3. The administration of DES in the concentrations used cannot prevent an initial rise of T in the serum. Clinical results of this study will be presented in session III of this symposium.

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A DEPOT LH-RH AGONIST (ICI-118630) AS PRIMARY TREATMENT OF ADVANCED CARCINOMA OF PROSTATE.

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From January 1984 to February 1986, 37 patients have been treated with a Depot LH-RH agonist (Zoladex) as primary treatment of advanced carcinoma of prostate.
Twenty two patients (Group I) received monthly injections of Zoladex. Mean follow up is 12 months (range : 3 - 24). Fifteen patients (Group II) received in addition diethylstilboestrol t.i.d. one week prior and one week after the first depot injection. Mean follow up is 5 months (range 3-9).

RESULTS

In Group I : 19/22 patients are evaluable (3 dropping out : 1 death and 2 patients lost to follow up). In Group II : 12/15 patients are evaluable (1 patient lost to follow up and 2 patients with a follow up < 3 months). Response to therapy was determined according to EORTC criteria.

Table : Group I (n=19) Group II (n=12) I+II (n=31)

	n	%	n	%	n	%
C.R.	0	-	0	-	0	-
P.R.	6	31	6	50	12	39
S.D.	10	53	5	42	15	48
P.	3	16	1	8	4	13
	19		12		31	

Conclusion

LH-RH agonists are an effective treatment of advanced prostatic carcinoma. In the short term, objective response rates appear to be similar to those of orchiectomy.

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CLINICAL RESULTS AND ENDOCRINOLOGICAL EFFECTS OF ZOLADEX (ICI 118.630), AN LH-RH ANALOG, IN THE TREATMENT OF ADVANCED PROSTATE CANCER: RESULTS OF A MULTI-INSTITUTION FRENCH STUDY

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A total of 85 previously untreated patients with advanced prostate cancer were entered in this study. Mean patient age was 70.8 years (range 45-88). Only 58 of these patients are currently evaluable. Patients received daily subcutaneous injections of 250 µg Zoladex until October 1984, after which the agent was administered in 3.6 mg subcutaneous sustained release form every 28 days. After 4 weeks of treatment, mean serum LH and FSH were suppressed below pretreatment values; mean serum testosterone (T) was in the range of values observed in surgically castrated men. Serum LH, FSH and T remained suppressed for as long as therapy was continued(max. follow-up 47 weeks). The objective response rate for the 58 evaluable patients included : partial regression 57%, stable disease 14%, progressive disease 29%. Forty-nine patients were symptomatic before treatment; the subjective improvement rate was 45% (22/49) as assessed by a symptom scoring system and 71% (35/49) by the clinician's assessment. Median time to progression was 22 weeks. Eight patients experienced hot flushes; two had breast tenderness. Seven patients complained of increased bone pain during the first month of treatment; this was transient in 5 patients, but the other 2 had rapidly progressive skeletal metastases. No clinical, hematological or biochemical side-effects requiring the discontinuation of Zoladex were observed. Comparison of castration results in the literature and the findings of this study demonstrate the efficacy and safety of Zoladex in the management of advanced prostate cancers.

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TREATMENT OF ADVANCED PROSTATIC CANCER WITH A DEPOT FORMULATION OF D-TRP 6-LH-RH. A MULTICENTRIC PHASE II TRIAL.

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95 untreated patients(pts)with stage C and D prostatic ca.were treated for up to 24 mos(median 16 mos)with the long acting D-TRP 6-LH-RH.The drug was injected i.m.every 4 wks.Treatment produced a significant decrease of LH levels and suppression of testosterone(T)within the 3rd wk.T remained within castrate levels in the followup.86 pts are currently(february 86)evaluable for overall response according to the NPCP-USA criteria.In C and D1 group(n=33) 69.7% showed partial response(PR),27.3% were stable(S), and 3% progressed(P).In D2 group(n=53)figures were 37.7%,49.1% and 13.2% respectively.Response in different involved sites below:

	PROSTATE	(%)	NODES	(%)	BONE	(%)
CR	1/90	(1.1)	5/17	(29.4)	-	-
PR	43/90	(47.8)	6/17	(35.3)	7/53	(13.2)
S	45/90	(50.0)	6/17	(35.3)	38/53	(71.7)
P	1/90	(1.1)	-	-	8/53	(15.1)

Actuarial survival(700 days)in the 86 pts was 78.5% and median progression free survival was 15 mos.In D2 pts median progression free survival was 370 days,while it was not yet reached in C and D1 pts.In most cases treatment produced relief of bone pain and of urinary symptoms.Side effects related to the decrease of T were observed in about half of pts.No disease "flare" occurred in our series.The slow release preparation of D-TRP 6-LH-RH offers an important alternative in the management of advanced prostatic carcinoma.