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PROMETHEUS, the Titan who stole fire from Heaven and gave it to Mankind, presides over the elegant lower plaza of New York City's Rockefeller Center. The 18 foot high bronze statue, designed by Paul Manship, hovers over a cascading fountain.

(Photo courtesy of New York Convention Bureau)

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EFFECTIVE SUSTAINED ANDROGENIC SUPPRESSION WITH (D-Nal(2)^6), NAFARELIN ACETATE: A NEW INTRANASAL FORM OF LHRH AGONIST. Suhayl Kalash and Mario Eisenberger*, Baltimore, MD; Milan Henzl* and Philip Hoffman*, Palo Alto, CA (Presentation to be made by Dr. Kalash)

To test the efficacy of an intranasal LHRH agonist, 122 patients with previously untreated stage D_2 prostate CA were randomized on to an ongoing trial comparing (D-Nal(2)^6)-LHRH (nafarelin acetate, Syntex Research) at a dose of 0.3 mg by intranasal spray BID, to DES, 1 mg p.o. TID. Effective long term testosterone (T) suppression to limits of detectability was achieved with nafarelin. Mean (T) values:-baseline-4.8 ng/ml; first week - 6.7ng/ml; week 4-0.3 ng/ml and 6 mos-0.2 ng/ml. Mean values with DES were:-baseline 4.3 ng/ml; first week-1.5 ng/ml; week 4 - 0.4 ng/ml and 6 mos - 0.3 ng/ml. In patients receiving treatment for long periods of time (median follow-up 219 days), no (T) elevations were observed after morning nafarelin doses. The major cardiovascular complications (myocardial infarction, pulmonary embolus, acute thrombo-phlebitis, deep vein thrombosis, and congestive heart failure) requiring early discontinuation of treatment occured only on the DES arm. One patient on nafarelin developed mild transient epistaxis which did not require treatment modification and another was switched to subcutaneous nafarelin due to compliance problems. Fifty-eight patients have been randomized to nafarelin and 64 to DES. Similar objective/subjective response rates were seen in both arms. With a median F/U of 6 mos (1-14 mos), 82% and 76% of the nafarelin and DES patients respectively continue on treatment without evidence of disease progression.

Nafarelin has a low incidence of toxicity and no major compliance problems. Contrary to previous reports on another intranasal LHRH agonist, nafarelin produces sustained suppression of (T) to the limits of detectability. Clinical benefits thus far seem comparable to DES and other forms of parenteral LHRH analogs. Intranasal administration of such compounds should enhance their attractiveness for clinical use by circumventing the need for daily subcutaneous administration. Further patient accrual and long term follow-up are needed to determine effect on disease free and overall survival.

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KETOCONAZOLE HIGH DOSE (H.D.) IN THE MANAGEMENT OF METASTATIC PROSTATIC CARCINOMA. Frans M.J. Debruyne, Fred J. Witjes* and the members of the Dutch South-East Cooperative Studygroup. (Presentation to be mady by Dr. Debruyne)

Ketoconazole H.D. inhibits testosterone production in both the testes and adrenals and has therefore been recently advocated for the treatment of prostate cancer. 79 patients (pts) with histologically proven metastatic carcinoma of the prostate were treated with Ketoconazole H.D.. 40 pts were untreated, 18 pts had one hormonal treatment and 21 pts had several hormonal therapies before starting ketoconazole H.D. Two treatment regimes were compared: 3 x daily 400 mgr (48 pts) and 2x daily 600 mgr (31 pts) of a Ketoconazole suspension. RESULTS: Pretreated group: Objective response: (EORTC criteria) in 60% of the pts stable disease and in 40% progression at 6 months. Subjective response (WHO criteria) was seen in 54% of the symptomatic patients (36 pts). Untreated group: Objective response: CR, PR and SD was seen in 29 pts (73%) at 6 months and progression in 11 pts (27%). Subjective improvement occured in 82% of the symptomatic pts. Castration level of testosterone was obtained in all patients within 2 days. Endocrinologically a further decrease in testosterone from 35 ng/dl (mean +SD) to 20 ng/dl (mean + SD) within 2 days was seen in both therapy arms. (castration level 30 ngr/dl) Side effects: No adrenal insufficiency or hepatic toxicity was observed. Major toxicity signs were gastro-intestinal disturbances (nausea-vomiting) which occured in 35% of the pretreated patients and 26% of the non-pretreated group.

Conclusion: Ketoconazole H.D. is effective in the treatment of patients with prostatic cancer. In addition, it had a marked subjective effect in hormonally pretreated patients.

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FLUTAMIDE IN THE TREATMENT OF ADVANCED PROSTATE CANCER. Michael A. Keating*, Pamela P. Griffin*, Stephen F. Schiff* Boston, MA. (Presentation to be made by Dr. Keating)

A twelve year experience with the oral non-steroidal anti-androgen Flutamide (750 mg qd) allows an assessment of its efficacy as therapy for advanced prostatic carcinoma. Of 80 patients entered in an open study, 69 were evaluable. Of these, 53% (37) achieved complete remission (CR) demonstrating total subjective response, normal serum acid phosphatase (SAP), cessation of hydronephrosis and improved or stable bone surveys. Partial remission (PR) showing subjective responses without normalized objective parameters occurred in 23% (16) patients. Failure of therapy was seen in another 16 patients. The average duration of response until progression of disease was 28.9 mos. for CR and 12.8 mos. for PR. Correlation of treatment and tumor grade showed CR in 43% (19/44) poorly differentiated, 68% (13/19) moderately differentiated and 100% (5/5) well differentiated primaries. Tumor burden (as a function of T stage, SAP, and bone surveys) also correlated with response showing CR in 22% (7/31) of severely, 68% (17/25) moderately and 100% (13/13) mildly afflicted patients. Flutamide was used as an alternative to diethylstilbesterol (DES) in 10 patients actively responding to DES but unable to tolerate its side effects. A continuation of CR (avg. 33.6 mos.) was seen in all 10 cases. Of another 7 patients failing DES, only 1 achieved CR. Significantly, libido was preserved in 80% (29/36) of instances. Other side effects noted were gynecomastia 68% (47), altered liver function (3), methemoglobulinemia (2) and emesis (2). One death from hepatic failure occurred. These findings suggest Flutamide may be an effective alternative to conventional hormonal therapy in the primary treatment of advanced prostatic carcinoma and has encouraged a randomized, prospective study presently underway.

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COMBINED TREATMENT WITH FLUTAMIDE IN ASSOCIATION WITH MEDICAL OR SURGICAL CASTRATION. F. Labrie, A. Dupont, Y. Lacourciere, M. Giguere, A. Belanger, G. Monfette and J. Emond

One hundred and nineteen previously untreated patients having clinical stage D_2prostate cancer received the combined treatment with the non-steroidal antiandrogen Flutamide in association with orchiectomy (13 patients) or the LHRH agonist (D-Trp^6) LHRH ethylamide (106 patients). The duration of treatment is 515 days (100 to 1156 days). A positive objective response assess according to the criteria of the US National Prostatic Cancer Project has been observed in 115 out of 119 patients (96.6%). Pain was initially present in 64% of patients and disappeared in all of them during the first month of treatment. Serum prostatic acid phosphatase was elevated in 85% of cases and returned to normal in 95% of cases. Complete, partial and stable responses have been obtained in 29 (24%), 45 (37.8%) and 41 (34.5%) of patients, respectively. Of the 15 deaths, 9 (7.6%) were due to prostate cancer while 6 (5%) resulted from other causes. The probability of positive response after two years of treatment (according to Kaplan and Meier) is 60% while the probability of survival at the same time interval is 88%. This probability of survival should be compared to the rate of 40 to 60% observed with treatments limited to inhibition of testicular androgen secretion or action (by surgical or medical castration). The present data show that the combined treatment in stage D_2 prostate cancer shows advantages as compared to previous therapies. In terms of percentage of positive objective response at the start of treatment, duration of remission, survival and quality of life. The death rate is in fact decreased by 300% during the first two years of treatment while the side effects are limited to hot flashes and a decrease or loss of libido. It is most important to start the administration of the antiandrogen at the same time as surgical or medical castration.