J. Steroid Biochem. Molec. Biol. Vol. 37, No. 6, pp. 961–963, 1990
Printed in Great Britain.

0960-0760/90 $3.00 + 0.00

TREATMENT OF NEWLY DIAGNOSED STATE D2 PROSTATE CANCER WITH LEUPROLIDE AND FLUTAMIDE OR LEUPROLIDE ALONE, PHASE III, INTERGROUP STUDY 0036

E. DAVID CRAWFORD* and JUDITH A. ALLEN
Division of Urology, University of Colorado Health Sciences Center, Denver, CO 80262, U.S.A.

Summary—In order to test the hypothesis of complete androgen blockade for advanced prostate cancer (D_2CaP), an intergroup trial was instituted in 1985 comparing leuprolide (L) alone to the combination of L with flutamide (F). Eligibility requirements included previously untreated histologically confirmed stage D_2CaP, measurable bone or soft tissue metastases, performance status (PS) of 3 or better, acceptable renal and hepatic function, no severe cardiac disease, and no prior or concomitant endocrine therapy. Stratification at entry was on the basis of PS and none or minimal disease (MD) versus severe degree (SD) of bone metastases. Six hundred and seventeen patients were entered into this study between March 1985 and April 1986. At the present time, there is a 3-month difference in the median progression-free survival (13.9 vs 16.9 months; $P = 0.039$) and a 7.1-month difference in survival (27.9 vs 35.01 months; $P = 0.035$) favoring L + F. In L + F-treated patients with good PS-MD, the median survival recently has been reached and is 51.9 months vs 39.6 months for L + P patients. The 107 black patients in the study had median survival of 26.4 months vs 33.3 months for whites. Discussions of racial differences in survival as well as other prognostic factors will be presented. The combination of L + F is superior to treatment with L alone. The benefits appear greatest in patients with minimal disease.

Prostate cancer has become the leading cause of cancer-related deaths in males in the United States. In 1990 alone, it is estimated that over 100,000 cases of prostate carcinoma will be diagnosed and that more than 28,000 men will die of the disease. More than 50% of men diagnosed with prostate cancer already have locally advanced or metastatic disease at the time of presentation and diagnosis.

Traditional therapy for prostate cancer has included medical or surgical castration to interrupt the production of the male hormone testosterone on which cancer cell growth is dependent. Testosterone is generated and controlled by the hypothalamus, pituitary, testis, and adrenal glands. The hormone-dependent nature of prostate cancer was demonstrated in the 1940s and has since been investigated through a number of therapies that have been effective in eliminating or reducing the androgens of gonadal origin, thus reducing prostate cancer cell growth [1]. These therapies have included surgical castration, estrogen therapy, and recently, non-steroidal antiandrogens. Antiandrogens are effective in blocking the androgen action at the cellular level.

Flutamide is one of the antiandrogens that has been proven to effect a high level of antitumor activity for metastatic prostate cancer when administered with leuprolide acetate [2]. This combined therapy neutralizes both adrenal and gonadal androgens [3]. The efficacy of this combined androgen blockade therapy was tested in a multi-institutional clinical trial sponsored by the National Cancer Institute. [4]. The double-blind, placebo-controlled, randomized trial compared flutamide and leuprolide with flutamide and placebo to test the effectiveness of combined androgen blockade in men with metastatic prostate cancer who had received no prior therapy.

Ninety-three institutions in the United States participated in the study affiliated with five cooperative groups, including the National Prostatic Cancer Project (NPCP), Southwest Oncology Group (SWOG), Northern California

*Proceedings of the 2nd International EORTC Symposium on "Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti-)Steroidal Agents", Rotterdam, The Netherlands, 9–11 April 1990.

*To whom correspondence should be addressed: Professor E. David Crawford, Division of Urology, University of Colorado Health Sciences Center, Campus Box C-319, 4200 East Ninth Avenue, Denver, CO 80262, U.S.A.

Oncology Group, North Central Cancer Group, and the Mid-Atlantic Oncology Program with the SWOG serving as coordinating office and statistical center. Study accrual was initiated in January 1985 and completed in April 1986 with the achievement of the study accrual goal of 600 registrants. Patient eligibility requirements included previously untreated histological stage D2 prostate cancer with bone or measurable soft tissue metastasis, ECOG performance status (PS) of 0–3, acceptable kidney and hepatic function, and no evidence of cardiovascular disease. Exclusions included prior chemotherapy, hormone ablation biologic response modifiers, and other active neoplasms.

Initial baseline evaluations were performed that included complete blood count; urinalysis; serum testosterone, acid phosphatase, and alkaline phosphatase levels; and renal and hepatic function tests. Additionally, chest X-ray, bone scan, and computed tomography (CT) scan were used to evaluate metastasis. Following these evaluations, patients were registered and randomized to a treatment arm. Initial stratification was according to performance status with a PS of 0–2 in one group and a PS of 3 in another group. Patients were stratified also by minimal or severe extent of disease. Minimal disease was defined as the absence of disease in ribs, lung, long bones, skull, or soft tissue other than lymph nodes with severe disease indicating metastasis to any of these areas.

After treatment initiation, clinical evaluations were conducted at weeks 1 and 4; and laboratory studies were repeated at 4-week intervals. Complete laboratory, clinical and imaging evaluations were performed at 12-week intervals for the study duration.

Responses were evaluated according to the National Prostatic Cancer Project criteria. Patients in whom 1 or 2 new bone lesions were seen and who were subjectively stable at the initial 12-week evaluation were continued on an additional 6 weeks of therapy. If no further progression was seen on a second bone scan, the patient was considered stable and therapy was continued as assigned initially.

When disease progression was apparent according to study parameters, the treatment was unblinded. Patients randomized to placebo were given flutamide in addition to leuprolide and those randomized to flutamide were withdrawn from the study to be treated by the investigator. All patients are being following until death.

Survival was the study endpoint, with secondary endpoints of response to therapy and time to disease progression. A total of 617 patients were registered; however, 14 patients were subsequently deemed ineligible according to study parameters. Of the 603 eligible patients, 303 were randomized to receive flutamide and leuprolide and 300 to receive leuprolide and placebo. Study dosage was leuprolide 1 mg per day subcutaneously and either flutamide 250 mg orally three times a day or placebo tablets. The most commonly reported side effects in the combination therapy arm included nausea, vomiting, diarrhea, gynecomastia, peripheral edema, and hot flushes. However, none of these side effects were significant enough to warrant major treatment alteration or study withdrawal.

Response to therapy was evaluable in 280 of the patients (92%) receiving combination therapy and in 269 patients (89%) receiving monotherapy. Twenty-two of the 280 patients (7.9%) receiving flutamide and leuprolide and 19 of the 269 patients (7.1%) receiving leuprolide and placebo were reported to achieve complete response. Partial responses were seen in 100 of the 280 patients (35.7%) receiving combination therapy and in 76 of the 269 patients (28.2%) receiving leuprolide and placebo.

While the response to therapy differences were not significant, the difference in progression-free survival favoring the combination therapy was statistically significant. The leuprolide/flutamide arm had a median length of survival of 35.0 months, and the leuprolide/placebo arm had 27.9 months median length of survival. The most significant differences in progression-free survival and over-all survival were seen in patients with minimal disease and ECOG performance status 0–2. It should be noted, however, that the number of patients in these subgroups was small; namely, 41 in the leuprolide/flutamide arm and 41 in the leuprolide/placebo arm.

Additionally, it was found that median survival of blacks was less than for non-blacks, 26.4 months vs 33.3 months, respectively. It is evident that black race is an important prognostic factor for survival when performance status and extent of disease are the only factors under consideration but is not significant when other, more precise prognostic factors are considered.

With the life expectancy of the American male increasing and the population of older men growing, the incidence of prostate cancer is also

rising. Thus, it is evident that continued, concerted efforts to find treatment regimens that are effective are of paramount importance.

REFERENCES

1. Huggins C. and Hodges C. V.: Studies in prostatic cancer. I. The effects of castration, of estrogen, and of androgen injection on serum phosphatascs in metastatic carcinoma of the prostate. *Cancer Res.* **1** (1941) 293–297.
2. Neri R. and Kassem N.: Biological and clinical properties of antiandrogens. In *Hormones and Cancer 2: Proc. of the Second Int. Congr. on Hormones and Cancer. Progress in Cancer Research and Therapy.* (Edited by F. Bresciani, R. J. B. King, M. E. Kippman, M. Namer and J.-P. and Raynaud). Raven Press, New York. (1984) pp. 507–518.
3. Labrie F., DuPont A., Lacourcicrc Y. *et al.*: Combined treatment with flutamide in association with medical or surgical castration. *J. Urol.* **135** (Suppl.) (1986) (Abstr. 203A).
4. Crawford E. D., Eisenberger M. A., McLeod D. G. *et al.*: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *New Engl. J. Med.* **321** (1989) 419–424.