VOL 19, NO 1 JANUARY 1, 2001

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

ASCO
www.asco.org
Lippincott Williams & Wilkins

JOURNAL OF CLINICAL ONCOLOGY

The Official Journal of the American Society of Clinical Oncology

Journal of Clinical Oncology (ISSN 0732-183X) is published 24 times a year, twice monthly, by Lippincott Williams & Wilkins, 12107 Insurance Way, Hagerstown, MD 21740. Periodical postage is paid at Hagerstown, MD, and at additional mailing offices.

POSTMASTER: ASCO members send change of address to American Society of Clinical Oncology, 1900 Duke Street, Suite 200, Alexandria, VA 22314. Non-members send change of address to *Journal of Clinical Oncology,* c/o Lippincott Williams & Wilkins, PO Box 350, Hagerstown, MD 21740-0350.

Editorial correspondence should be addressed to George P. Canellos, MD, *Journal of Clinical Oncology,* 1900 Duke Street, Suite 200, Alexandria, VA 22314. Telephone: (703) 797-1900; FAX: (703) 684-8720. Email: jco@asco.org. Internet: http://www.jco.org

American Society of Clinical Oncology-related questions should be addressed to ASCO, 1900 Duke Street, Suite 200, Alexandria, VA 22314. Telephone: (703) 299-0150; FAX: (703) 299-1044. Email: asco@asco.org. Internet: http://www.asco.org

Correspondence regarding subscriptions or change of address should be directed to *Journal of Clinical Oncology,* Lippincott Williams & Wilkins, PO Box 350, Hagerstown, MD 21740-0350.

Japan: Orders should be placed through LWW Igaku-Shoin Ltd, 3-23-14 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Telephone: 3-5689-5400; FAX: 3-5689-2760. Email: yhirano@lwwis.co.jp. **India, Pakistan, Sri Lanka, Bangladesh, Nepal:** Orders should be placed through Globe Publication Pvt Ltd, B-13, 3rd Floor, A Block, Shopping Complex, Naraina Vihar, Ring Road, New Delhi 110028, India. Telephone: 11-5790212; FAX: 11-5798876. Email: jaideep.globe@axcess.net.in.

Change of address notices, including both the old and new addresses of the subscriber and the mailing label, should be sent at least one month in advance.

Customer Service: 1-877-734-3512

Yearly subscription rates: United States and possessions: individuals, $301.00; institutions, $419.00; students and residents, $118.00; single issues, $44.00. All other countries: individuals, $423.00; institutions, $541.00; students and residents, $142.00; single issues, $44.00. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Publication Mail Agreement Number 863289.

Prices are subject to change without notice. Current prices are in effect for back volumes and back issues. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. Back issues sold in conjunction with a subscription are on a prorated basis. *1999 bound volume price:* $100.00; $120.00 for international orders. To purchase a 1999 bound volume, customer must be a subscriber for 1999.

Advertising representative: Greg Pessagno, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Telephone: 410-528-4218.

Flutamide Versus Prednisone in Patients With Prostate Cancer Symptomatically Progressing After Androgen-Ablative Therapy: A Phase III Study of the European Organization for Research and Treatment of Cancer Genitourinary Group

By S. D. Fosså, P. H.Th. Slee, M. Brausi, S. Horenblas, R. R. Hall, J. W. Hetherington, N. Aaronson, L. de Prijck, and L. Collette

Purpose: **Time to progression (TTP), overall survival, and quality of life (QL) were compared in patients with hormone-resistant prostate cancer (HRPC) treated with prednisone (5 mg orally, four times a day) or flutamide (250 mg orally, three times a day).**

Patients and Methods: **Symptomatic patients were randomized to receive either prednisone (101 patients) or flutamide (100 patients). Subjective response was assessed based on performance status, the use of analgesics, and the need to apply alternative palliative treatment. Prostate-specific antigen (PSA)–based biochemical response (≥ 50% reduction of baseline PSA) was recorded. At baseline and at 6-week intervals during follow-up, patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30.**

Results: **There was no difference between the groups in median TTP (prednisone, 3.4 months; flutamide, 2.3 months) or overall survival (prednisone, 10.6 months; flutamide, 11.2 months). In the prednisone group, 56% of the patients experienced a subjective response, compared with 45% in the flutamide group ($P = .18$). The median response duration was 4.8 months for prednisone and 4.2 months for flutamide. A biochemical response was observed in 21% and 23% of the prednisone and flutamide groups, respectively. Gastrointestinal toxicity was the reason for trial discontinuation in seven patients receiving flutamide and two patients receiving prednisone. The QL assessment parameters favored the use of prednisone with statistically significant differences in pain, fatigue, role functioning, appetite loss, gastrointestinal distress, and overall QL.**

Conclusion: **In symptomatic HRPC, treatment with prednisone or flutamide leads to similar rates of TTP and overall survival and no difference in subjective or biochemical response. The QL results favor the use of low-cost prednisone in patients with HRPC.**

J Clin Oncol 19:62-71. © 2001 by American Society of Clinical Oncology.

APPROXIMATELY 70% to 80% of patients with advanced prostate cancer respond initially or remain stable when treated by medical or surgical castration, but in 20% to 30% of the patients, the malignancy progresses despite primary androgen deprivation. In addition, disease will progress in 60% to 80% of the responding patients during the first 3 years after the start of treatment.[1-3] In a recent meta-analysis, the addition of an antiandrogen to initial androgen suppression (total androgen blockade [TAB]) was shown to have a limited effect, if any at all.[4]

If the malignancy progresses despite androgen ablation after castration, three biologically different subgroups of hormone-resistant prostate cancer (HRPC) can be identified.

1. *HRPC with residual androgen sensitivity.* The cancer cells are still sensitive to residual circulating androgens produced mainly in the adrenal glands, and the malignancy may respond beneficially if the effect of these remaining androgens is removed. This can be achieved by medical suppression of adrenal corticosteroid production or, if not used previously, by the application of antiandrogens which block the androgen receptors of the cancer cells.

2. *Hormone-sensitive HRPC:* The disease is no longer androgen-sensitive, but it may still be influenced by hormones such as medroxy-progesterone acetate or high-dose estrogens.

3. *Androgen- and hormone-refractory HRPC:* The disease has become completely hormone-insensitive. Chemotherapy or investigational treatment modalities may be considered.

From the Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, Oslo, Norway; St Antonius Hospital, Nieuwegein, and Netherlands Cancer Hospital, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands; San Raffaele, Milan, Italy; Freeman Hospital, Newcastle, and Princess Royal Hospital, Hull, United Kingdom; and European Organization for Research and Treatment of Cancer Data Center, Brussels, Belgium.

Submitted March 24, 2000; accepted July 17, 2000.

Supported by grants no. 5U10 CA11488-11 through 5U10 CA11488-29 from the National Cancer Institute, Bethesda, MD.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Address reprint requests to Sophie D. Fosså, MD, Department of Oncology, Norwegian Radium Hospital, Ullernchausseen 70, 0310 Olso, Norway; email s.d.fossa@klinmed.uio.no.

0732-183X/01/1901-62

In the individual patient with HRPC, most often a mixture of these three cell populations is present in unknown proportions. Patients with prostate cancer who progress after primary androgen deprivation present with increasing somatic and psychologic distress, including pain due to bone metastases, anemia, and fatigue. Ten percent to 20% of the patients develop micturition problems caused by a growing primary tumor. Radiotherapy and analgesics can relieve local symptoms, but effective systemic therapies are needed to slow down or reverse the progressive development of the malignancy.

Several end points can be considered during the treatment of HRPC: overall survival, time to progression (TTP), objective response, physician-assessed subjective response, and quality of life (QL).

The evaluation of objective response according to the World Health Organization (WHO) criteria[5] is problematic because only 10% to 20% of the patients have easily measurable metastatic lesions. Objective response based on assessment of bone scans is also difficult due to frequent interobserver and interexamination variation.[6] Relief of metastatic bone pain and improvement of the patient's general condition are the most important parameters of subjective response in patients with HRPC and should be recorded routinely. During recent years, patient-based monitoring of QL has been introduced into clinical oncology, and appropriate questionnaires have been developed.[7] Biochemical response based on measurements of serum prostate-specific antigen (PSA) should be monitored as a separate entity. A recent consensus meeting has published guidelines for the evaluation of PSA-based response, thereby enabling more uniform reporting of observed changes.[8] In addition to the above methodologic problems, trials of chemotherapy to treat HRPC have been hampered by relatively frequent toxicity problems in the elderly prostate cancer patients who often present with major comorbidity. In this situation, it seems reasonable to influence the disease with hormones as long as possible, because hormonal manipulation is easily applied and has limited toxicity.

Surgical and medical adrenalectomy, the latter by hydrocortisone or prednisone, has been used in the treatment of HRPC for many years[9,10] to suppress the adrenal production of androstenedione and dehydroepiandrosterone. Up to the early 1990s, however, only a few well-designed phase II or III studies were published that evaluated medical adrenalectomy in HRPC.

Flutamide exhibits antiandrogenic effects by binding to the cellular androgen receptors and thus reducing the cell's androgen uptake. This drug has been used extensively in previously untreated patients, as a part of TAB or as monotherapy.[1,3,11] In limited series, flutamide has also been evaluated in the treatment of HRPC, with subjective response rates of 15% to 30%.[12,13]

In 1990, the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group initiated a phase III study to compare the effectiveness of prednisone and flutamide as secondary hormone manipulation in patients with metastatic HRPC. At that time, the expectation was that flutamide would be more effective than prednisone because of its specific activity in the cancer cell. The present report represents the final analysis of this study.

PATIENTS AND METHODS

Patients with histologically confirmed prostate cancer were eligible for the trial if they fulfilled the following criteria: (1) presence of symptomatic metastatic disease that had progressed after medical castration with luteinizing hormone-releasing hormone (LHRH) analogs (not estrogens) or bilateral orchiectomy. The pretrial serum testosterone level had to be within the range of the institution's castration levels. In the present study, symptomatic disease implied cancer-induced deterioration of the patient's general condition and/or painful, progressive metastatic disease with or without the use of analgesics, with or without complete pain relief; (2) WHO performance status of 0 to 3; (3) no previous use of prednisone, flutamide, or any other oral antiandrogen, but patients were eligible if they had received an antiandrogen transiently (for a maximum of 4 weeks) during their LHRH treatment in order to prevent a flare reaction; (4) no previous systemic anticancer treatment, except the above primary hormonal manipulation; and (5) certainty of clinical disease progression after prior surgery or previous radiotherapy. The patients were not allowed to receive radiotherapy at the time of trial entry.

Patients with a second primary tumor (except basal cell skin cancer), serious cardiovascular problems, or insulin-dependent diabetes mellitus were ineligible for the trial, as were those who were unable to comply with regular follow-up.

The trial was approved by the institutions' local ethical committee, and patients provided written informed consent before randomization. The trial was open for patient entry from January 1992 to March 1998. In October 1995, an independent data-monitoring committee approved continuation of the trial without modification. At the time of the present analysis, the median follow-up was 330 days.

Trial Design

Patients were randomized to receive either flutamide 250 mg orally three times a day (the F group) or prednisone 5 mg orally four times a day (the P group). Patients receiving LHRH analogs continued with this treatment.

All patients were examined for acute toxicity 3 weeks after trial entry. Response was evaluated at 6-week intervals from the start of treatment. Patients had to remain in the trial for at least 6 weeks to be assessable for response. They were otherwise included in the analysis as "non-assessable." Patients who progressed during the first 6 weeks were included in the progression category. Patients remained on the trial until subjective progression or unacceptable toxicity was recorded or until they wished to discontinue participation for any reason. Therapeutic interventions in patients who had gone off protocol treatment were chosen by the individual clinical investigator. All patients were followed until death.

At trial entry and at each follow-up visit, patients underwent a clinical examination, including assessment of pain using a five-point scale (level 0, analgesics not required; level 1, nonnarcotic analgesics occasionally required; level 2, nonnarcotic analgesics regularly required; level 3, oral or parenteral narcotic analgesics occasionally required; level 4, oral or parenteral narcotic analgesics regularly required). Types and doses of the prescribed analgesics were recorded. A chest x-ray and radioisotope bone scan were mandatory; other radiologic examinations were optional. "Superscan" was defined as ≥ 75% metastatic involvement of the central skeleton.

Blood samples were taken for analysis of hemoglobin, WBC count, and thrombocytes, together with the determination of PSA, alkaline phosphatase, creatinine, liver enzyme, and testosterone levels.

Clinical examinations and blood tests were repeated at each follow-up visit. Patients' performance status, weight, and degree of vomiting and diarrhea were recorded using the WHO criteria for toxicity.[5] The performance of other tests was left to the discretion of the clinical investigator.

Quality of Life

QL, as assessed by the patient, was a secondary end point of the study, but there was no a priori stated hypothesis. Thus, the QL evaluation was exploratory, with global QL representing the primary variable.

At trial entry and at each follow-up visit, patients were asked to complete the EORTC Quality of Life Questionnaire (QLQ) C-30 (version 1.0).[7] The QLQ C-30 is a 30-item questionnaire that was developed to assess a range of physical, emotional, and social health issues relevant to a broad spectrum of cancer patients. It has been shown to be reliable and valid in a wide range of patient populations and treatment settings and is currently being used in a large number of oncology clinical trials. The questions are organized into a number of multi-item scales and single-item symptom measures (five functioning scales [physical, role, cognitive, emotional, and social], three symptom scales [fatigue, nausea and vomiting, and pain], and six single items [assessing dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact]). The last two questions ask patients to rate their overall health and QL. The QLQ C-30 was supplemented by three questions pertaining to analgesic use (Did you take any medication for pain? If so, how much did it help? Have you had pain despite the use of analgesics?). All scales and single-item measures were linearly transformed to a 0 to 100 scale.[14] For the functioning scales and the global QL scale, a higher score represents a higher level of functioning/QL; for the symptom measures, a higher score corresponds to a greater degree of symptoms.

Response Criteria

Objective response was not assessed. On the basis of the physician's evaluation, three categories for subjective response were defined: response, no change, and progression. No minimum duration of response was required.

Response. At least one of the following three conditions had to be fulfilled: (1) reduction of the pain score (WHO criteria) by at least one level, with no deterioration of performance status; (2) unchanged pain level and reduction of the prescribed daily dose of analgesics by at least 25% as compared with the pretreatment situation, with no deterioration of performance status; and (3) improvement of the WHO performance status by at least one level without either an increase of the daily dose of analgesics by ≥ 25% or an increase in the pain level.

No change. "No change" was defined as an unchanged pain score, with less than a 25% reduction in the prescribed daily analgesic dose as compared with the pretreatment situation, and unchanged performance status.

Progression. Progression was evaluated relative to the best condition, observed at start of treatment or obtained during treatment. Progression was determined to have occurred if patients met at least one of the following conditions: increase of the pain score by at least one level, increase of the daily analgesic dose by at least 25%, any need to give additional pain treatment, such as radiotherapy, and WHO performance status deterioration by at least one level.

Duration of subjective response was calculated from trial entry to the date of progression. Biochemical response was defined as a decrease of the serum PSA level by ≥ 50% as compared with the baseline value.[8,15] However, no duration was required for biochemical response.

Statistics

The main end points for this trial were TTP and duration of survival. Since virtually all patients entered onto the trial were expected to progress and die during follow-up, either of these end points could be chosen for calculating the sample size. A total of 192 patients followed until death were required in order to detect a difference of 50% in the median duration of survival between the two treatment arms (from 9 months with prednisone to 13.5 months with flutamide), using a two-sided log-rank test (alpha = 0.5, beta = 0.20). Two hundred patients were sufficient to detect a difference of 20% in the response rate in the two arms (alpha = 0.05, beta = 0.20).

Given an anticipated median survival time of 8 to 10 months (based on the published literature on HRPC) and the number of available observations at each subsequent assessment point, the QL analysis was restricted to the 6-month period following entry onto the study. Means and confidence intervals were calculated for the QL scores of both treatment groups at each assessment point, yielding a series of descriptive profiles that could be displayed in graphic form. In order to adjust for multiple comparisons over time, 99% confidence intervals were calculated to maintain an overall 95% confidence interval for each QL outcome. A linear mixed model analysis of variance was used that accounts for serial correlations between observations, as well as for intermittent missing forms. The main effects of treatment and time were tested on a reduced model (without an interaction term) whenever the interaction effect was found not to be statistically significant.

The intention-to-treat principle was followed in all statistical analysis (ie, including ineligible and nonassessable patients in the analysis and considering patients in the treatment group they were allocated to by randomization).

RESULTS

Patients

A total of 201 patients were randomized to receive prednisone (101 patients) or flutamide (100 patients, Table 1). Presumed prognostic factors and comorbidities were equally distributed between the two treatment groups ($P > .05$). Almost all patients used analgesics, with approximately 25% regularly using narcotics for pain level 4. The median number of hot spots on bone scans was 12 in both groups, and approximately 25% of the patients displayed superscans. The initial PSA level was elevated to more than

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.