The Use of Flutamide in Hormone-refractory Metastatic Prostate Cancer

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In a recent intergroup study under the auspices of the National Cancer Institute, 603 eligible patients with newly diagnosed disseminated adenocarcinoma of the prostate were prospectively randomized in a double-blinded clinical trial to receive either a gonadotropin-releasing hormone analogue (leuprolide) and a nonsteroidal antiandrogen (flutamide) or leuprolide and placebo. Of the 603 eligible patients, 300 were in the leuprolide and placebo arm and 303 were in the leuprolide and flutamide arm. At the time of disease progression, the code was broken: Those patients in the placebo arm were given the opportunity to receive flutamide, and the patients in the flutamide arm were treated at their physician’s discretion. There was no survival time distribution difference, based on survival measured from the progression data, between the patients who were received flutamide after progression and those who were treated at their physician’s discretion after progression. Furthermore, the addition of flutamide to leuprolide at the time of disease progression resulted in a survival-time distribution that is similar to other treatments of hormone-refractory prostate cancer. Cancer 1993; 72:3870-3.

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Androgen deprivation has been the mainstay of treatment for patients with metastatic prostate cancer. The rationale for this treatment is based on the work of Huggins and Hodges in 1941.1 Sixty to eighty percent of prostate cancer patients will show subjective and objective improvement with orchiectomy or estrogen. Recently, the use of gonadotropin-releasing hormone analogues has shown similar results.2 Regardless of the method, the median time to progression with hormonal therapy is 12-18 months, and median survival time ranges from 24 to 30 months. Patients with minimal disease and good performance status received a more striking benefit with maximal androgen ablation. Previously unreported is our analysis of the impact of flutamide on survival of those patients who in whom leuprolide and placebo failed compared to those in whom the combination therapy of leuprolide and flutamide failed and then were treated with various modalities, such as chemotherapy.

Materials and Methods

The concept of total androgen blockade in the treatment of metastatic prostate cancer was tested recently in the United States by Crawford et al.3 The trial was conducted as a collaborative intergroup study with participation by the following groups: the National Prostatic Cancer Project, the Southwest Oncology Group, the Northern California Oncology Group, the North Central Cancer Treatment Group, and the Mid-Atlantic Oncology Program.# The major contributors to the National Cancer Institute Intergroup Study (INT-0036) were the following: the Southwest Oncology Group—Charles A. Coltman, Jr., M.D. (University of Texas, San Antonio, Texas), Janice Takashima and Debbie Spicer (Statistical Center, Seattle, Washington), James Montie, M.D. (Cleveland Clinic, Cleveland, Ohio), and Joseph Drago, M.D. (Ohio State University, Columbus, Ohio); the National Prostatic Cancer Project—Gerald P. Murphy, M.D. (State University of New York, Buffalo, New York), Brian J. Miles, M.D. (Henry Ford Hospital, Detroit, Michigan), Mitchell C. Benson, M.D. (Columbia-Presbyterian Medical Center, New York), and Joseph Drago, M.D. (Ohio State University, Columbus, Ohio); the National Prostatic Cancer Project—Gerald P. Murphy, M.D. (State University of New York, Buffalo, New York), Brian J. Miles, M.D. (Henry Ford Hospital, Detroit, Michigan), Mitchell C. Benson, M.D. (Columbia-Presbyterian Medical Center, New York).
The purposes of the postprogression treatment option in the placebo arm were to provide patients on placebo access to flutamide and to generate descriptive information about the initiation of flutamide at progression.

Some treating physicians did not register a patient’s progression immediately after it began; however, these progression registration delays were regarded as minor protocol violations. The criterion for a progression registration delay was a lack of registration within 60 days after a patient’s progression. Patients with progression registration delays or no progression registration are not included in this analysis. In the case of a progression registration delay, the Southwest Oncology Group Statistical Center became aware of the progression through normal data submission channels and then contacted the treating physician. An audit of a sample of 25 registration progression delays was performed: In eight cases the statistical center discovered the criteria for progression were met before the progression was reported through registration. In 14 of the 25 audited cases, the treating physician declared an earlier date for progression based on confirmatory follow-up tests, and the remaining 3 cases were simple administrative delays.

At the time of this analysis, 347 patients had disease progression followed by a period of survival. Of these 347 patients, 72 patients had progression registration delays as defined in the previous paragraph, while 14 were either unblinded before progression (i.e., the drug was determined because diarrhea occurred before progression) or had recent progression. The remaining 261 patients had progression registrations within 60 days after progression and compose the study group of patients used in the analysis in this article.

Results

Of the 261 study group patients, 128 were randomized to the leuprolide plus placebo arm, and 133 were randomized to the leuprolide plus flutamide arm. In this paper, these subgroups will be designated as the ON subgroup and the OFF subgroup, respectively, to indicate the intent for continued protocol treatment (flutamide for the former and no further protocol treatment for the latter). It is necessary to identify postprogression treatments by intent because the submission of detailed treatment, response, or progression data for the postprogression period was not required for patients in the OFF group. An audit of 55 cases in the OFF group was performed to ascertain what immediate postprogression treatment was initiated: 16 patients received no further treatment; 12 patients had bilateral orchietomy as further hormonal therapy; 4 patients received diethylstilbestrol as further hormonal therapy; 4 patients...
were treated with 5-flourouracil; and postprogression treatment could not be ascertained for 4 patients.

The submission of notices of death after progression was required for all patients, and all treating physicians were sent periodic reminders of the need for survival data. Therefore, the date of death (the outcome of primary interest) was rigorously assessed.

The data were analyzed using Cox regression and the Kaplan–Meier method for the display of failure-time data. Figure 1 is a Kaplan–Meier plot of survival from the date of progression for the two subgroups. The survival time distributions of the ON and OFF subgroups were not significantly different (Cox regression). The estimated ON over OFF death-hazard rate ratio was 0.95, with a 95% confidence interval from 0.74 to 1.22 (a death-hazard rate ratio of unity indicates equal death-hazard rates). The estimates of median postprogression survival (with 95% confidence intervals) were 12.3 months (10.3–14.8) and 11.8 months (10.4–14.0) for the ON and OFF subgroups, respectively.

Additionally, Cox regression was used to build models of postprogression survival with other covariates that had potential prognostic importance for postprogression survival time. None were significant, and neither the randomization stratification classification (severe versus minimal disease) nor the time to original progression were related to postprogression survival, a finding that was particularly noteworthy.

Discussion

Patients who fail to respond to endocrine therapy have few viable therapeutic options available to them. It has been reported that median life expectancy at the time of progression is usually 6 months or less. Several earlier studies that used flutamide in untreated advanced disease reported promise for the use of this compound in this clinical situation. Based in part on these studies, the National Prostatic Cancer Project, between 1984 and 1985, randomized 220 hormone-refractory patients to receive either flutamide or estramustine phosphate, but this study showed no difference in response between these two drugs. The quest has been, and is, to find some agent(s) that will have therapeutic value at the time of progression. There occasionally have been reports of a subjective response from a variety of agents; however, evaluation of secondary treatment in hormone-refractory patients is complicated by various factors. Because the majority of patients' prostate cancer disease metastasizes to bone, and only rarely are the metastases bidimensional or else measurable by visceral or nodal disease, measurement is problematic. In addition, the sometimes "stable" nature of the disease compounds the problems of measurement.

This difficulty in the lack of measurable disease and the difficulty of assessment have been cited by MacFarlane and Tolley. The authors of this study reported disease stabilization in 6 of 17 patients treated with flutamide but noted that the responses were short-lived and should not be regarded as evidence of efficacy. They felt that flutamide was of little value in patients in whom hormonal manipulation had failed.

In a study by Sogani et al., only 6 of 26 patients with advanced disease after endocrine treatment showed a favorable response to flutamide. Stoliar and Albert reported that in their study, 7 of 18 patients responded, but they noted that 3 of their 7 responders had not received prior endocrine therapy.

Labrie et al., however, reported on 209 patients evaluated for their response to the addition of flutamide following progression of disease after previous treatment with diethylstilbestrol, orchietomy, or luteinizing hormone-releasing hormone. In their paper, the authors reported that 13 patients (6.3%) had a complete response, 20 (9.6%) had a partial response, 39 (18.7%) had an objectively stable response, and 137 (65.5%) continued to progress. In their data, the authors compared their patient population to a control group of patients in a report from the National Prostatic Cancer Project. Blumenstein has noted that comparing the former group with that in the National Prostatic Cancer Project study is problematic, because these two populations are from two different clinical resources.

Our data contradict the results of Labrie and his colleagues. Although our studies were not designed initially to study the effect of the addition of flutamide after progression, we were able to analyze precisely the
median time to death in the two groups of patients, 128 patients (ON subgroup) where the intent was further treatment with leuprolide plus flutamide, and 133 patients (OFF subgroup) who were off study and treated at the investigator's option. The term "off-study" means that the patient was found not to be on flutamide; however, the patient remained in the protocol as far as data collection was concerned.

Eisenberger et al. demonstrated that the survival of patients in studies on endocrine-resistant prostate cancer is poor. They documented that, in these studies, the median survival estimates from initiation of postprogression therapy range from 5 to 11 months. The median postprogression survival estimates for the ON and OFF subgroups in our analysis, 12.3 and 11.8 months, respectively, were consistent with the range reported by Eisenberger, because the median survivals from our data were based on the date on which progression was documented rather than the date on which postprogression therapy was initiated.

This analysis provides no evidence of flutamide efficacy following progression after hormonal therapy. The patient groups compared were not created by randomization, however, and therefore may not be fully comparable, especially because group membership was related to progression time. The authors are not aware of any published randomized comparisons addressing the issue of flutamide efficacy following progression. The strength of this study, in comparison to previously reported nonrandomized studies of this question, is that patients in our two groups came from the same patient population (i.e., patients who were randomized to the leuprolide plus flutamide group versus those randomized to the leuprolide plus placebo group).

The issue of the use of an antiandrogen following progression is not likely to be resolved by comparing nonrandomized studies. The authors therefore recommend that a randomized, double-blinded clinical trial of antiandrogen use following progression, with survival as the primary end point, be initiated. Such a study would have shorter duration than a study of newly diagnosed stage D2 patients, because survival is shorter. The main issue seems to be one of selecting the underlying therapy. Perhaps a study could be designed also to address the issue of continued androgen ablation following progression.

References


