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LONG-TERM EFFICACY AND SAFETY OF NILUTAMIDE PLUS CASTRATION IN ADVANCED PROSTATE CANCER, AND THE SIGNIFICANCE OF EARLY PROSTATE SPECIFIC ANTIGEN NORMALIZATION

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ABSTRACT

Purpose: We studied the long-term efficacy and tolerability of nilutamide, a nonsteroidal antiandrogen, combined with orchietomy in patients with advanced prostate cancer.

Materials and Methods: A large double-blind trial was done on 457 patients randomized to receive nilutamide or placebo after orchietomy.

Results: At 8.5 years of followup significant benefits were found for progression and survival in favor of patients receiving nilutamide and orchietomy. In addition, normalized prostate specific antigen levels at 3 months from the start of therapy were predictive of good long-term outcome. Moreover, combined androgen blockade with nilutamide increased the chance of patients having normal prostate specific antigen levels at 3 months. Nilutamide was well tolerated in the long term with no increase in the incidence of drug specific adverse events.

Conclusions: With long-term followup of patients with advanced prostate cancer, the combination of nilutamide and orchietomy has significant benefits in interval to progression and improved survival compared to orchietomy and placebo.

Key Words: prostatic neoplasms, orchietomy, prostate-specific antigen, hormones

Maximal androgen blockade, the addition of an antiandrogen to medical or surgical castration, represents a suitable improvement compared to castration alone in patients with advanced prostate cancer. Although castration leads to disease regression and, therefore, improved quality of life, prolonged survival is not evident. A possible explanation for this fact is that, although castration greatly decreases serum testosterone concentrations by approximately 90%, androgens of adrenal origin remain unaffected. However, the combination of an antiandrogen plus castration results in inhibition of androgens produced from testicular and adrenal sources.

The nonsteroidal antiandrogen nilutamide has proved to be effective in combination with castration for advanced prostate cancer. Double-blind comparative studies have indicated beneficial effects for nilutamide and orchietomy compared to orchietomy plus placebo with respect to best objective response, improvement in metastatic related pain and normalization of tumor markers. In addition, a significantly longer interval to objective or subjective progression for the nilutamide plus orchietomy group has been indicated in a double-blind study involving more than 400 patients. In this large study, in which patients were followed for at least 18 months, a trend towards prolonged survival was also observed. However, this advantage was not statistically significant even though the study was mature, since at least 50% of the patients had progression or died. These findings have been supported by a meta-analysis of 7 double-blind studies, including 1,056 evaluable patients, that showed statistically significant differences in favor of nilutamide and orchietomy for best objective response, improvements in bone pain, levels of tumor markers and disease progression. The odds of death from cancer and from other causes were also decreased in the nilutamide combination group but the difference was not statistically significant.

In the largest of the double-blind studies the followup currently is approximately 8.5 years, and we report on this second efficacy and safety analysis. The relationship between early normalization of prostate specific antigen (PSA) and disease progression in these patients is also examined (preliminary results have been reported previously) following indications that normalization of PSA, rather than simply a decrease, is predictive of improvement in the prognosis of advanced prostate cancer.

MATERIALS AND METHODS

A total of 457 patients with stage D2 prostate cancer was initially enrolled into this multicenter double-blind placebo controlled study. Following orchietomy the patients were randomized to receive 300 mg. nilutamide once daily for 1 month and then 150 mg. once daily (225) or identical placebo tablets (232). During the extended followup clinical and laboratory evaluations were repeated every 6 months. Objective progression was assessed using modified (more strict) National Prostatic Cancer Project criteria.

Patients continued taking the study drug or placebo until they had objective progression or intolerance, or withdrew consent. When progression occurred only patients who had been on nilutamide could continue with this drug on an open label basis to allow a comparison according to the initial randomization. Such patients were included in the safety analysis. All patients were followed until death. This second analysis was performed on 2 main efficacy criteria: 1) intervals to progression and 2) death. Safety was assessed by questioning patients in a general manner at each visit to determine whether any clinical adverse experience had occurred and by monitoring laboratory values. PSA was measured at a central laboratory using the Pros-Check PSA radioimmunooassay kit (upper normal value 2.5 ng./ml).
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PROTOCOL

A total of 519 patients were entered into the study. They were randomized in a 1:1:1 ratio into three treatment groups: nilutamide plus orchiectomy, placebo plus orchiectomy, and placebo alone. The primary objective of the study was to compare the efficacy of nilutamide plus orchiectomy versus placebo plus orchiectomy versus placebo alone in delaying the occurrence of disease progression or death from all causes. Treatment groups were further stratified on the basis of baseline clinical characteristics, including age, prostate-specific antigen (PSA) level, Eastern Cooperative Oncology Group (ECOG) performance status, and prior hormone therapy. If patients were stratified for both hormone therapy and PSA, treatment groups were further stratified by a weighted randomization scheme. This randomization ensured that the treatment groups were balanced at about 33% for both hormone therapy and PSA levels. Patients were considered evaluable for efficacy if they started nilutamide or placebo treatment and had a followup PSA measurement at least 6 months after treatment initiation. The number of evaluable patients was 317 in the nilutamide group, 316 in the placebo plus orchiectomy group, and 315 in the placebo alone group. All evaluable patients were included in the analysis of drug-related events and mortality regardless of treatment assignment. Patients were withdrawn from the study for reasons unrelated to treatment or study dropouts. Analysis of the intent-to-treat population was also performed. The primary endpoint of the study was the objective (evaluable) disease progression, defined as a 50% or greater increase in PSA level from the nadir or the occurrence of a new lesion. The secondary endpoints were time to disease progression, survival, and tolerability. A total of 272 patients were assessed for efficacy completely and without treatment assignment bias. No statistically significant differences were observed in terms of patient and disease characteristics at study entry between the treatment groups. The median age was 63 years (range 48 to 79). The median duration of followup was 24 months for patients in the nilutamide plus orchiectomy and placebo plus orchiectomy groups, respectively, for a statistically significant difference (p = 0.024, part A of figure). This difference was confirmed and became statistically significant (p = 0.013) when all causes of death for all patients were considered the reference (part B of figure). At 6 years the survival rates were 32 and 21%, respectively. Median progression-free intervals were 32 and 21 months, respectively. This 6.5-month difference in interval to progression (44% improvement) was statistically significant (p = 0.002). Even after 5 years of therapy 20% of patients receiving nilutamide did not have progression compared to 12% receiving placebo. The progression-free actuarial survival rates for 8.5 years in evaluable patients were consistently greater in the nilutamide plus orchiectomy group than in the placebo plus orchiectomy group (part A of figure). Median intervals to progression were 21.2 and 14.7 months, respectively. This 6.5-month difference (44% improvement) was statistically significant (p = 0.002). Even after 5 years of therapy 20% of patients receiving nilutamide did not have progression compared to 12% receiving placebo.

DISCUSSION

At 8.5 years of followup of patients in a large, double-blind, randomized study orchiectomy combined with nilutamide resulted in statistically significant improvements in cancer survival (p = 0.013), overall survival (p = 0.033) and interval to progression (p = 0.002) compared to orchiectomy plus placebo. In an earlier (mature) analysis there was a significant difference (p = 0.005) in interval to progression and a trend towards improved survival. In both analyses the median interval to death from cancer was 37 months for the nilutamide group. However, with prolonged followup the difference was confirmed and became statistically significant. Moreover, the 6.5-month difference in interval to progression, reported here with extended followup, increased the greater in the nilutamide plus orchiectomy (59%) than in the placebo plus orchiectomy (28%) groups.
statistical significance found in the previous study (from \( p = 0.005 \) to \( p = 0.002 \)). It is noteworthy that patients who prematurely discontinued treatment because of adverse events were included in the analysis of interval to progression and censored at treatment discontinuation. Therefore the progression analysis was less likely to favor the nilutamide group, since the percentage of dropouts for adverse events was slightly greater in the nilutamide (19%) than in the placebo (12%) group. However, even with this unfavorable bias, interval to progression was significantly longer in the nilutamide group.

The a priori statistical determination of the power of the study was made under the assumptions that interval to objective progression for the placebo plus orchiectomy group would be 65 weeks and that 200 patients in each treatment group would have provided a 94% chance of detecting a 38% improvement in the median progression-free survival from 65 to 90 weeks at the 0.05 level of confidence. These assumptions were met and the clear benefit of adding nilutamide to castration has been demonstrated.

Nilutamide was generally well tolerated, and most of the adverse events reported were consistent with those found with other endocrine therapies. Moreover, with prolonged (5.5 years) exposure to nilutamide there were no increases in the number of specific adverse effects, for example problems with visual adaptation when changing from a bright light to a dark environment and interstitial pneumonitis. In the previous analysis visual disturbance was the second most frequent adverse event (after hot flushes), affecting 27% of patients receiving nilutamide combined with orchiectomy. Visual disturbances are generally mild and tend to disappear after the scheduled dosage reduction from 300 to 150 mg, or spontaneously, they only lead to approximately 2% of withdrawal from therapy and are always reversible on treatment discontinuation.\(^{2,5,6,10}\) Interstitial pneumonitis is a rare adverse event (1 of 225 patients in our study) and is reversible with discontinuation of nilutamide.\(^{2,11}\)

An extended follow-up, as in our study, allows for statistical confirmation of earlier trends in efficacy results and for assessment of the long-term safety of combined androgen blockade. Our efficacy results reported have followed a pattern similar to those for European Organization for Research and Treatment of Cancer study No. 30853, in which patients were randomized to receive combined androgen blockade (flutamide and a luteinizing hormone-releasing hormone analogue) or orchiectomy. In that study a follow-up of approximately 5 years indicated maximal androgen blockade to be statistically significantly better in terms of progression and duration of survival but, again, there had only been a trend to increased survival in a previous analysis.\(^{13}\)

Statistically significantly longer progression-free and median survivals have also been reported in a large National Cancer Institute study for flutamide and a luteinizing hormone-releasing hormone analogue, compared to a luteinizing hormone-releasing hormone analogue alone.\(^{14}\) In the National Cancer Institute study the benefits for maximal androgen blockade were most evident in patients with a good performance status and minimal disease. In contrast, other generally smaller studies have indicated no improvements in survival or interval to disease progression for maximal androgen blockade compared to castration.\(^{5,10,15-18}\)

In our study orchiectomy was chosen rather than luteinizing hormone-releasing hormone agonists not only to avoid any compliance problems relating to the method of castration but also to avoid disease flare found in up to 5% of patients receiving luteinizing hormone-releasing hormone agonists as monotherapy.\(^{19}\) This choice also allows the long-term efficacy of the androgen to be related to its self-effect rather than to the prevention of disease flare.

Early normalization of PSA was shown to predict an improved long-term response to hormonal treatment in terms of interval to disease progression and death. Nilutamide plus orchiectomy increased the chance of a patient having a normal PSA within 3 months of treatment and, therefore, improved the probability of longer progression-free interval and survival. This finding is consistent with the results of a previous study of nilutamide and a luteinizing hormone-releasing hormone analogue compared to the antiandrogen plus placebo, in which gains in median interval to progression and survival were reported in patients whose PSA was normalized by 3 months regardless of the treatment group.\(^{20}\)

Nilutamide, with its long plasma elimination half-life (56 hours), offers the convenience of a once daily dosing regimen.\(^{21}\) Although nilutamide was initially used in clinical studies in divided doses (every 8 hours), we have shown it to be effective and well tolerated as a single daily dose. Once daily dosing has obvious benefits in terms of compliance rather than 3 or 4 times daily schedules.\(^{22}\) Moreover, compliance is particularly important in the elderly, and prostate cancer mainly affects men older than 60 years.\(^{23}\)

**CONCLUSIONS**

The treatment of advanced prostate cancer is still only palliative. It is important to delay the progress of the disease and, therefore, maintain and/or improve the quality of life of patients for as long as possible. The long-term follow-up of patients with advanced prostate cancer has indicated significant benefits in interval to progression and also survival for a combined orchiectomy and nilutamide regimen compared to orchiectomy and placebo. Furthermore, the prognostic value of monitoring PSA early in therapy has been demonstrated on the outcome of disease in terms of survival and progression, possibly making PSA a surrogate marker of efficacy.

**REFERENCES**


