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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 orchiectomy 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 orchiectomy.

Results: At 8.5 years of followup significant benefits were found for progression and survival in favor of patients receiving nilutamide and orchiectomy. 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 orchiectomy has significant benefits in interval to progression and improved survival compared to orchiectomy and placebo.

KEY WORDS: prostatic neoplasms, orchiectomy, 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.[1,2] A possible explanation for this fact is that, although castration greatly decreases serum testosterone concentrations by approximately 90%, androgens of adrenal origin remain unaffected.[3,4] 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 orchiectomy compared to orchiectomy plus placebo with respect to best objective response, improvement in metastatic related pain and normalization of tumor markers.[1,2,5] In addition, a significantly longer interval to objective or subjective progression for the nilutamide plus orchiectomy group has been indicated in a double-blind study involving more than 400 patients.[6] 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 orchiectomy for best objective response, improvements in bone pain, levels of tumor markers and disease progression.[7] 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.

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In the largest of the double-blind studies the followup currently is approximately 8.5 years,[6] 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[8]) following indications that normalization of PSA, rather than simply a decrease, is predictive of improvement in the prognosis of advanced prostate cancer.[9]

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 orchiectomy 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[6] 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 radioimmunoassay kit (upper normal value 2.5 ng./ml.) be-

* Yang Laboratories, Inc., Bellevue, Washington.

fore treatment, at 1, 3 and 6 months after the start of treatment, and then at regular 6-month intervals.

Progression-free and survival actuarial rates were computed with the Kaplan-Meier estimate. The survival distribution of the 2 treatment groups was subjected to the log rank test. An intent-to-treat analysis was also performed on all patients studied.

RESULTS

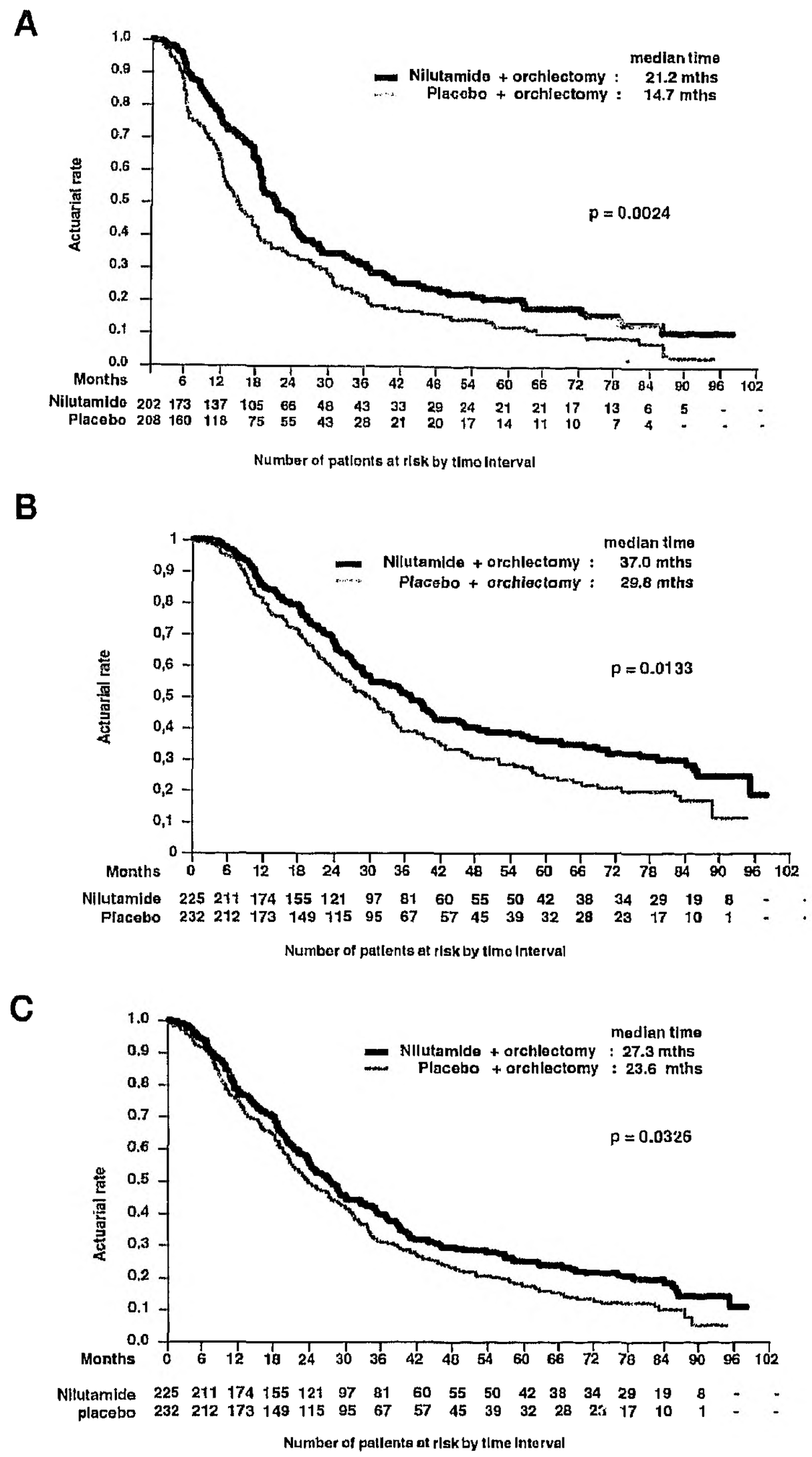
Patient and disease characteristics at study entry were similar between the 2 groups.[6] At the second cutoff date for data collection (December 31, 1994) followup ranged from 82 to 102 months, which was 55 months longer than that of the previous analysis of progression and 47 months longer than that for the previous analysis of survival.[6] Of the patients 283 were withdrawn from the study due to progression (127 in the nilutamide group versus 156 in the placebo group) and 70 due to intercurrent or adverse events (42, or 19% versus 28, or 12%, respectively).

Interval to progression. 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.

Interval to death. At 8.5 years of followup the median intervals to death from prostate cancer were 37.0 and 29.8 months for patients in the nilutamide plus orchiectomy and placebo plus orchiectomy groups, respectively, for a statistically significant ($p = 0.013$) difference of 7 months (24% increase, part *B* of figure). At 6 years the survival rates were 32 and 21%, respectively. When all causes of death for all patients were considered the 16% survival gain was still in favor of nilutamide plus orchiectomy ($p = 0.033$, part *C* of figure).

Tolerability. At the initial analysis 102 patients (45%) in the nilutamide plus castration and 89 (38%) in the castration alone groups had been followed for at least 18 months. After 7 to 8 years of followup 12 (5%) and 6 (2.5%) patients were still taking nilutamide or placebo, respectively. After 8.5 years of treatment the number of patients remaining in the study was low and may be seen on actuarial curves for progression (number of patients at risk). Despite this longer exposure to treatment, no new cases of drug specific adverse events were experienced, such as interstitial pneumonitis or visual disorder. Moreover, since the initial analysis only 7 patients from the nilutamide group and 8 from the placebo group discontinued treatment due to adverse or intercurrent events. Age related intercurrent events, not necessarily leading to study dropout, occurred with the same incidence in both treatment groups.

PSA. PSA levels were measured in 272 of the evaluable patients. Regardless of the treatment group, PSA levels were elevated in 97% of these patients at baseline. After 3 months of treatment PSA normalized in 121 patients (44%) and remained elevated in 151 (56%). No further improvements in PSA were observed after 6 months or longer of treatment. Patients whose PSA was normal at 3 months had significantly longer median intervals to disease progression ($p < 0.0001$) and death ($p < 0.0001$) than those with elevated PSA at 3 months. Median progression-free intervals were 24 versus 17 months, respectively, median interval to disease related death was 49 versus 28 months, respectively, and median interval to death from all causes (overall survival) was 37 versus 24 months, respectively ($p < 0.0001$). When PSA was analyzed by treatment the percentage of patients with normal PSA at 3 months was significantly ($p < 0.001$) greater in the nilutamide plus orchiectomy (59%) than in the placebo plus orchiectomy (28%) groups.



Actuarial survival rates. *A*, objective (evaluable) progression-free survival. *B*, prostate cancer survival (all patients). *C*, overall survival (all patients). *mths*, months.

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.[6] 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

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.[6] Moreover, with prolonged (8.5 years) exposure to nilutamide there were no increases in the incidences of specific adverse events, 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.[6] 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 withdrawals 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 followup, 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.[12] In that study a followup 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.[2,10,15–18]

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 antiandrogen 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 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 followup 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.

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