Long-term Results of Danish Prostatic Cancer Group Trial 86

Goserelin Acetate plus Flutamide versus Orchiectomy in Advanced Prostate Cancer

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In a multicenter trial conducted by the Danish Prostatic Cancer Group, 264 patients with advanced prostate cancer were randomized either to undergo bilateral orchiectomy or to receive combination treatment with goserelin acetate and flutamide. This report is an update of that study, covering a median follow-up for survival of 57 months. Of 262 patients who were evaluated, 208 have died. As noted in earlier analyses of this study, no differences in time to progression and cause-specific and overall survival could be identified between the two treatment groups. In conclusion, the combination of goserelin and flutamide was not clinically superior to bilateral orchiectomy in the treatment of advanced prostate cancer. ***Cancer*** **1993; 72:3851–4.**

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In 1986, the Danish Prostatic Cancer Group initiated a multicenter trial to test the hypothesis presented by Labrie et al. that complete androgen blockade is superior to surgical castration in the treatment of prostate cancer.[1] Eleven surgical and urologic departments participated in the trial. Details on study design and methods have been reported previously.[2,3] Data on adverse effects and subjective and objective response were presented in these earlier reports and have not changed. The purpose of this presentation is to give a long-term update on time to progression and survival.

Patients and Methods

During an 18-month inclusion period that began in June 1986, 264 patients with previously untreated, histologically verified, advanced prostate cancer were entered into the study. Of these patients, 262 were eligible to participate and could be evaluated for survival.

Patients were allocated by local block randomization either to undergo bilateral orchiectomy or to receive combination treatment with goserelin acetate (Zoladex R, Zeneca Pharmaceuticals, Alderly Park, Macclesfield, UK; 3.6 mg every 4 weeks) and flutamide (Eulexin R, Schering-Plough, Kenilworth, NJ; 250 mg three times daily).

The study's main end points were time to objective progression and survival. Evaluation of objective progression, according to the protocol, was discontinued 24 months after the last patient had entered the study. At that point, 80% of patients who could be evaluated had reached objective progression. Time to objective

Table 1. Causes of Death in 208 Patients

	Orchiectomy	Zoladex/flutamide
Prostatic cancer	90 (85)	87 (85)
Cardiovascular	5	7
Other malignancy	2	2
Infection	3	2
Suicide	1	—
Other, unknown	5	4
Total	106	102

Values are no. of patients (%).

progression was defined as time to progression, according to protocol criteria, or death (whichever came first) in the absence of a cause of death other than prostate cancer.

Toxicity and subjective and objective response to therapy also were also assessed and already have been reported in detail.[2,3] Similarly, details on eligibility, ineligibility, evaluation, and follow-up, as well as criteria for objective and subjective response, have been reported.[2]

A sample size of at least 120 patients in each treatment arm was chosen to provide a 90% probability of detecting a 20% increase in objective response rate at a significance level of 0.05.

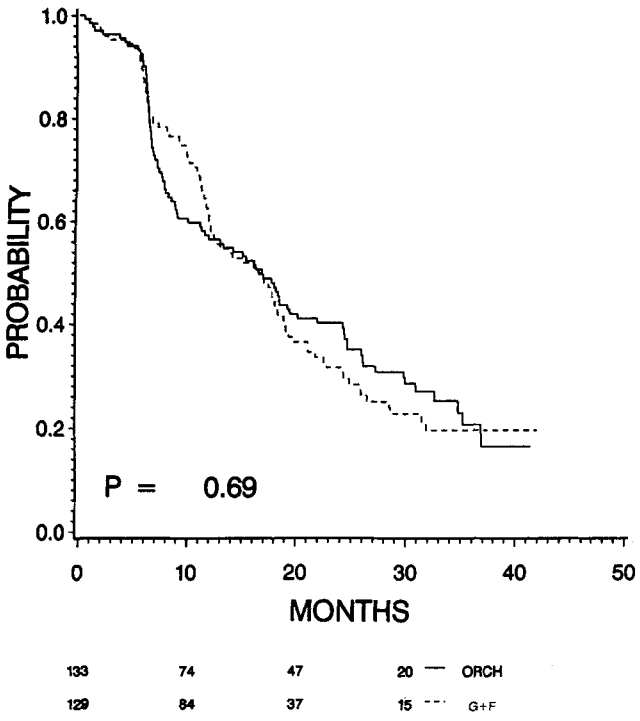

Figure 1. Time to progression defined as time to either objective progression or death from prostate cancer (whichever came first). Median time to progression was 16.8 months in the orchiectomy group and 16.5 months in the goserelin plus flutamide-treated group.

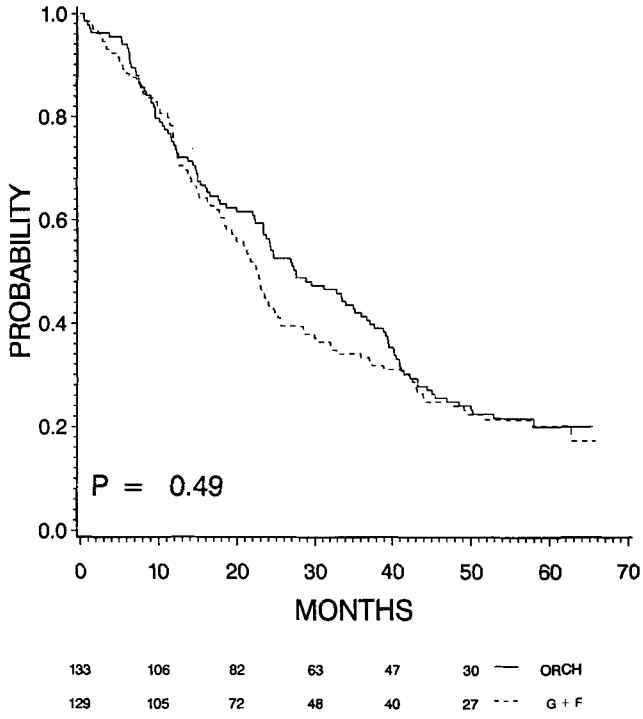

Figure 2. Survival in all 262 patients regardless of cause of death. Median survival in the orchiectomy group was 27.6 months and in the goserelin plus flutamide group, 22.7 months. A total of 208 patients have died, 177 of prostate cancer.

Survival curves and time to progression curves were calculated according to the Kaplan–Meier product-limit method and were compared using the log-rank test.[4] P values and patients at risk are listed in the figures, which are discussed in detail below.

Results

At the time of entry, patient characteristics and prognostic factors were well balanced between the two treatment arms. Detailed tables have been presented earlier.[2] The large majority of patients had distant metastases, but 24 (9%), 15 and 9 in the two treatment groups, respectively, had only locally advanced disease (T-category 3/4 and/or lymph node metastasis).

Median follow-up for survival is 57 months, and 262 patients can be evaluated for survival: 133 in the orchiectomy group and 129 in the goserelin and flutamide-treated group. Of 231 patients who are no longer in the study, 208 died, the majority because of prostate cancer (Table 1). Time to progression and overall survival of the two treatment groups are displayed in Figures 1 and 2. Survival curves for deaths caused by prostate cancer only are shown in Figure 3. No statistically significant differences in time to progression and overall or cause-specific survival were identified.

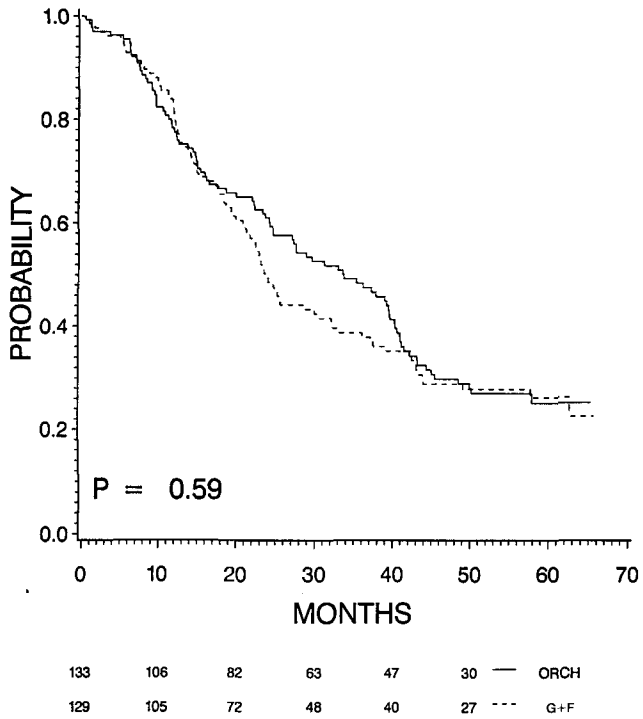

Figure 3. Cause-specific survival including only deaths from prostate cancer. In the orchiectomy group, 90 of the patients (85%) died of prostate cancer, and in the goserelin and flutamide group 87 of the patients (85%) died of prostate cancer.

At the time of entry, 73 patients fulfilled the criteria of having "minimal disease" as defined by Crawford et al.: "Absence of disease in ribs, long bones, skull, or soft tissue, other than lymph node involvement."[5(p. 421)] Figures 4 and 5 show time to objective progression and cause-specific survival, respectively, for this patient category, according to treatment arm, and compare them with the remaining patients who had "severe" disease (i.e., those who had metastases in some or all of the mentioned sites). As expected, patients with minimal disease had significantly longer progression-free and cause-specific survival than did patients with severe disease ($P < 0.001$). However, no differences could be demonstrated between treatment arms.

Discussion

As reported earlier, the combination of goserelin and flutamide in this study resulted in a small but statistically significant difference in objective response compared with bilateral orchiectomy. On the other hand, more adverse effects were associated with the combination therapy, and no differences in subjective response to therapy, either in quality or duration, could be established.[2,3]

The current update covers approximately 5 years of follow-up for survival and concurs with earlier analyses.[2,3] No benefit in terms of longer progression-free, cause-specific, or overall survival is evident in the group of patients receiving the combination therapy compared with the patients treated with orchiectomy.

The National Cancer Institute-sponsored, double-blind Intergroup study randomized more than 600 stage M1 patients to receive leuprolide plus flutamide or leuprolide plus placebo.[5] A recent update on survival showed an approximately 20% gain in overall survival in the flutamide-treated group.[6] Discussions about to what extent the flare phenomenon observed in the leuprolide plus placebo group may have contributed to this difference have complicated interpretation of the study. A new, large-scale National Cancer Institute-sponsored trial comparing orchiectomy plus placebo with orchiectomy plus flutamide is in progress (MA Eisenberger, M.D. personal communication, 1992).

In the Intergroup trial, the benefit of the combined treatment seemed most pronounced in the group of patients with minimal disease.[5] We were not able to con-

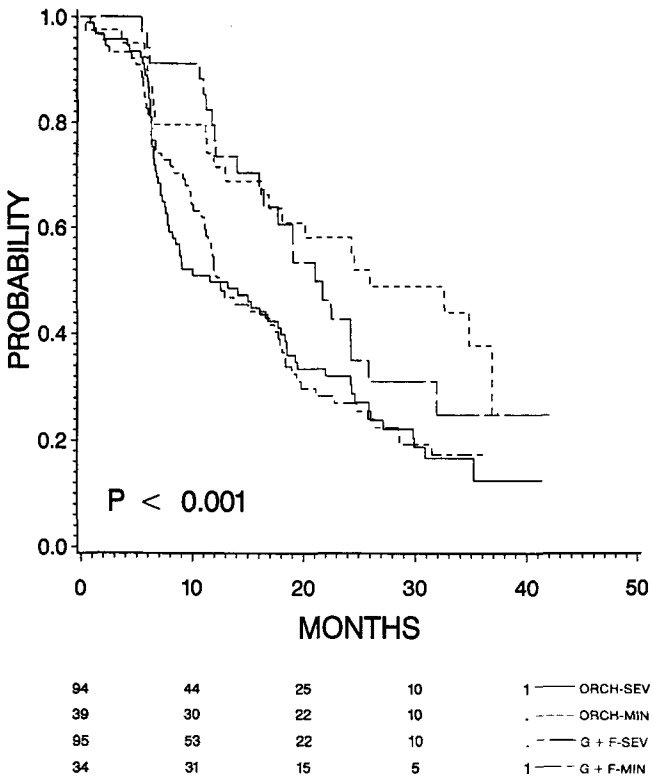

Figure 4. Time to objective progression (or death from prostate cancer, whichever came first) in 73 patients with minimal disease (39 and 34 in the orchiectomy and combination arms, respectively) compared to 189 patients with severe disease (94 and 95 in the two arms, respectively). The difference between minimal and severe disease was statistically significant. However, no significant differences could be identified between treatment regimens.

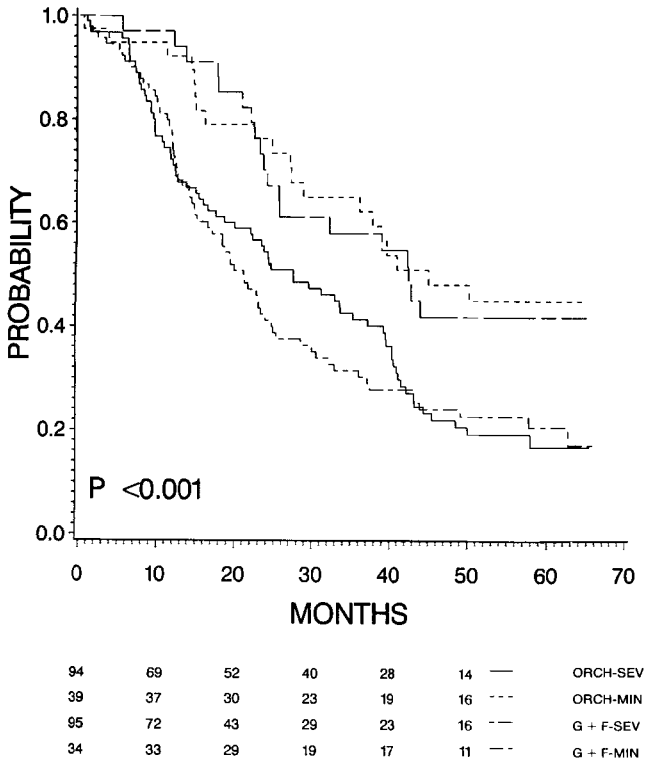

Figure 5. Cause-specific survival including only deaths from prostate cancer in 73 patients with minimal disease (39 and 34 in the orchiectomy and combination arms, respectively) compared to 189 patients with severe disease (94 and 95 in the two arms, respectively). The difference between minimal and severe disease is statistically significant. However, no significant differences could be identified between treatment regimens.

firm this in our study, where, retrospectively, a group of patients was identified as fulfilling the criteria for minimal disease.

The EORTC 30853 study, which has a design almost identical to that in the present study, is presented elsewhere in this issue.[7] Based on a median follow-up for survival of 3 years, the EORTC study has found statistically significant, longer times of progression-free and cause-specific survival in favor of the combination of goserelin and flutamide over orchiectomy. How two studies as identical in design as DAPROCA 86 and EORTC 30853 can differ so remarkably in their results is not understood easily.

However, the DAPROCA study was designed when it was suggested that complete androgen blockade could lead to remarkable improvement in rate and duration of response. The sample size of that study was not calculated to detect differences in overall survival in the range of 20%, which the National Cancer Institute Intergroup study found.[6] Thus, the risk of overlooking a survival benefit of that size is not insignificant in our study. This risk of this type-2 error is estimated to be approximately 50%.

Therefore, even though our study did not find the combination treatment with goserelin and flutamide to be superior to orchiectomy, the issue of a possible benefit of complete androgen blockade in the treatment of prostate cancer is still unsettled. The result of a metaanalysis of randomized studies on this subject is eagerly awaited.[8]

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