The FinnProstate Study VII: Intermittent Versus Continuous Androgen Deprivation in Patients With Advanced Prostate Cancer

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
CAD = continuous androgen deprivation
IAD = intermittent androgen deprivation
LHRHa = luteinizing hormone-releasing hormone analogue
OS = overall survival
PC = prostate cancer
PCS = prostate cancer specific survival
PFS = progression-free survival
PSA = prostate specific antigen
TF = treatment failure
TOFF = treatment off period
TON = treatment on period
TTF = time to treatment failure

Purpose: We conducted a randomized trial to compare intermittent and continuous androgen deprivationin patients with advanced prostate cancer. We studied time to progression, overall and prostate cancer specific survival, and time to treatment failure.
Materials and Methods: Between May 1997 and February 2003, 852 men with locally advanced or metastatic prostate cancer were enrolled to receive androgen deprivation therapy for 24 weeks. Patients in whom prostate specific antigen decreased to less than 10 ng/ml, or by 50% or more if less than 20 ng/ml at baseline, were randomized to intermittent or continuous androgen deprivation. In the intermittent therapy arm androgen deprivation therapy was withdrawn and resumed again for at least 24 weeks based mainly on prostate specific antigen decrease and increase.
Results: There were 298 patients who did not meet the randomization criteria. The remaining 554 patients were randomized, with 274 (49.5%) to intermittent androgen deprivation and 280 (50.5%) to the continuous androgen deprivation arm. Median followup was 65.0 months. Of these patients 392 (71%) died, including 186 (68%) in the intermittent androgen deprivation arm and 206 (74%) in the continuous androgen deprivation arm ($p = 0.12$). There were 248 prostate cancer deaths, comprised of 117 (43%) in the intermittent androgen deprivation and 131 (47%) in the continuous androgen deprivation arm ($p = 0.29$). Median times from randomization to progression were 34.5 and 30.2 months in the intermittent androgen deprivation and continuous androgen deprivation arms, respectively. Median times to death (all cause) were 45.2 and 45.7 months, to prostate cancer death 45.2 and 44.3 months, and to treatment failure 29.9 and 30.5 months, respectively.
Conclusions: Intermittent androgen deprivation is a feasible, efficient and safe method to treat advanced prostate cancer compared with continuous androgen deprivation.

Key Words: prostatic neoplasms, androgens, testosterone

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ANDROGEN deprivation therapy has been the standard treatment for advanced prostate cancer since the 1940s.[1] Despite the initial response, many patients are likely to experience significant adverse effects.[2,3] Although enthusiasm increases for intermittent androgen deprivation to optimize the ADT efficacy while minimizing adverse effects, only a few published randomized trials concern IAD in the treatment of prostate cancer as summarized in a review by Abrahamsson.[4]

The FinnProstate Study VII, a randomized multicenter trial, was planned to compare the efficacy of intermittent vs continuous androgen deprivation in the treatment of PC with time to progression as the primary end point. Secondary objectives were to compare the treatment arms in terms of overall survival, PC specific survival and time to treatment failure (ie withdrawal from the trial). Our interim analysis showed that patients with a high tumor burden, high PSA or widely metastasized disease failed to show an adequate biochemical PSA response to ADT, and were not candidates for IAD[5] in accordance with others' findings.[6–8] Concerning IAD the 2 essential questions addressed by the FinnProstate Study VII are 1) does IAD delay the onset of hormone resistance? and 2) can IAD improve overall survival?[9]

MATERIALS AND METHODS

The FinnProstate Study VII was conducted as an open label, randomized, controlled parallel group multicenter clinical trial at 27 clinics in Finland comparing intermittent vs continuous androgen deprivation in patients with histologically confirmed, locally advanced or metastatic PC (Appendix 1). Study inclusion criteria were M1 disease at any PSA, M0 disease at PSA 60 ng/ml or greater, or T3-4M0 prostate cancer at PSA 20 ng/ml or greater, or previously surgically or radiotherapy treated localized prostate cancer and PSA recurrence of 20 ng/ml or greater; no previous hormonal or medical treatment for PC; and performance status 0–2 with a life expectancy of at least 12 months. Ethics committees in each center approved the trial protocol and amendments. All patients gave written informed consent. The study is registered with ClinicalTrials.gov, identifier NCT00293670.

The study was originally designed to enroll patients with metastatic PC. However, to increase recruitment, the inclusion criteria were widened in June 1998 to include patients with locally advanced or recurrent PC without metastases. With this more heterogeneous patient population, the primary analysis was meant to be completed 14 months later than the specified 36 months. Median time to progression (the primary objective) was estimated as 20.5 months, with a total of 600 patients (300:300) required to detect a hazard ratio of 1.345 with 90% power for CAD vs IAD. The final study visit was in January 2010.

All patients recruited received the LHRHa goserelin acetate (3.6 mg) subcutaneously every 28 days for 24 weeks (run in) before randomization. The antiandrogen cyproterone acetate was given in 100 mg twice daily during the first 12.5 days to minimize flare reaction. Patients in whom PSA decreased to less than 10.0 ng/ml or at least by 50% (baseline PSA less than 20.0 ng/ml) were randomized to IAD or CAD at a 1:1 ratio by using the rand function of Excel®. In the CAD arm patients continued with goserelin acetate or underwent bilateral orchiectomy. In the IAD arm LHRHa was withheld after randomization and was resumed, including flare protection with cyproterone acetate, for at least 24 weeks whenever PSA increased more than 20.0 ng/ml or above the baseline value, and was withheld again by the same criteria as for randomization. LHRHa was continued if PSA did not decrease to less than 10.0 ng/ml or decreased less than 50% of baseline. From the randomization forward, the treatment cycle (duration in weeks) was defined as time off treatment plus time on treatment. Time to progression, treatment failure and death were calculated from the date of randomization.

The patient was withdrawn from the trial if any criterion for TF was fulfilled. The criteria for TF and disease progression are listed in Appendix 2. Any progression criterion met during TOFF was considered real progression if initiation of ADT failed to relieve the symptoms. After withdrawal, patients were treated according to investigator's decision (eg maximal ADT, chemotherapy etc). Thereafter, patients were followed every 12 weeks until progression and every 24 weeks until death.

Student's t test, the median test or the chi-square test was used in comparing patient characteristics between treatment arms. PFS, OS and PCS were analyzed using a univariate unadjusted Cox model, and graphically displayed by the Kaplan-Meier method. The hazard ratios were estimated together with the associated 95% CI and p value. Statistical tests were 2-sided at a 5% significance level.

RESULTS

Between May 1997 and February 2003, 852 patients were prospectively enrolled to receive ADT. After the run in period 298 (35%) patients failed to meet the randomization criteria and were excluded from study. The remaining 554 (65%) patients were randomized as 274 (49.5%) to the IAD and 280 (50.5%) to the CAD arm. No patients with recurrent PC after prostatectomy or radiotherapy were enrolled in the study. Median followup from randomization was 65.0 months (maximum 11.6 years). No patients were lost to followup. There were 110 patients who continued for more than 5 years in the trial before TF, including 52 (19.0%) in the IAD and 58 (20.7%) in the CAD arm ($p = 0.50$). Mean patient age was 71.5 years, with no difference in distribution of patients by age group (younger than 50, 50 to 59, 60 to 69, 70 to 79, 80 years or older). Treatment arms were comparable in terms of advancement of PC, differentiation grade, performance status, concurrent diseases and PSA (table 1). Of these randomized patients 79% achieved a PSA nadir of 4 ng/ml or less. One patient refused the randomized IAD.