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Survival benefit of early androgen receptor inhibitor therapy in locally advanced prostate cancer: Long-term follow-up of the SPCG-6 study

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Abstract ***Background:*** The optimal timing of endocrine therapy in non-metastatic prostate cancer (PCa) is still an issue of debate.
Methods: A randomised, double-blind, parallel-group trial comparing bicalutamide 150 mg once daily with placebo in addition to standard care in patients with hormone-naïve, non-metastatic PCa. Kaplan–Meier analysis was used to estimate overall survival (OS) and multivariate Cox proportional hazard model was performed to analyse time-to-event (death).
Findings: A total of 1218 patients were included into the Scandinavian Prostate Cancer Group (SPCG)-6 study of which 607 were randomised to receive bicalutamide in addition to their standard care and 611 to receive placebo. Median follow-up was 14.6 years. Overall, 866 (71.1%) patients died, 428 (70.5%) in the bicalutamide arm and 438 (71.7%) in the placebo arm, $p = 0.87$. Bicalutamide significantly improved OS in patient with locally advanced disease (hazard ratios (HR) = 0.77 (95% confidence interval (CI): 0.63–0.94, $p = 0.01$), regardless of baseline prostate-specific antigen (PSA), with a survival benefit which was apparent throughout the study period. In contrast, survival favoured randomisation to the placebo arm in patients with localised disease (HR = 1.19 (95% CI: 1.00–1.43), $p = 0.056$). However, a survival gain from bicalutamide therapy was present in patients with localised disease and a baseline PSA greater than 28 ng/mL at randomisation. In multivariate Cox

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proportional hazard model, only including patients managed on watchful waiting as their standard of care ($n = 991$) OS depended on age, World Health Organisation (WHO) grade, baseline PSA, clinical stage and randomised treatment.

Interpretation: Throughout the 14.6 year follow-up period the addition of early bicalutamide to standard of care resulted in a significant OS benefit in patients with locally advanced PCa. In contrast, patients with localised PCa and low PSA derived no survival benefit from early bicalutamide. The optimal timing for initiating bicalutamide in non-metastatic PCa patients is dependent on disease stage and baseline PSA.

1. Introduction

Two randomised studies, COU-AA-302 and PREVAIL, have recently shown that androgen synthesis inhibition (abiraterone acetate) and inhibition of androgen receptor signalling (enzalutamide) can increase overall survival (OS) in patients with chemo-naïve metastatic castration resistant prostate cancer (PCa) [1,2]. The efficacy of these new compounds in hormone-naïve PCa is currently investigated in phase II + III trials [3] (ClinicalTrials.gov identifier: NCT01715285). Although endocrine manipulation is not first line therapy in non-metastatic PCa [4], this new development has documented that endocrine manipulation may prolong survival and it revives the old controversy of what constitutes the optimal timing of endocrine manipulation in management of PCa [5].

The Scandinavian Prostate Cancer Group (SPCG)-6 study was conducted as a randomised, double-blinded, placebo-controlled trial in Denmark, Finland, Norway, and Sweden. The SPCG-6 study was one of three trials included in the Early Prostate Cancer (EPC) programme evaluating the efficacy of bicalutamide 150 mg/day in addition to standard care in patients with hormone-naïve, non-metastatic PCa [6]. Previous separate analyses of the SPCG-6 trial indicated that the efficacy of bicalutamide depended on clinical stage and baseline prostate-specific antigen (PSA) at randomisation [7,8]. Patients with locally advanced (tumour category (T) 3–4, any N; or any T, N+) PCa randomised to bicalutamide had a significant improvement in progression-free survival (PFS) and OS, while survival non-significantly favoured placebo in patients with localised PCa (T1–2, N0/NX).

We report long-term survival update of the SPCG-6 study with a median follow-up of 14.6 years and an overall mortality rate of 71%.

2. Materials and methods

2.1. Study details

A detailed methodology of the SPCG-6 study has been described previously [7,9]. Between October 1995 and July 1998, 1218 males aged 18–75 years were included in 62 Nordic centres. Eligible patients had histologically confirmed localised (T1–2, N0/NX) or locally advanced (T3–4, any N; or any T, N+) hormone-naïve PCa with no evidence of distant metastases. Histological evaluation was performed according to the World Health Organisation (WHO) criteria. Their standard care before randomisation is listed in Table 1.

Patients were randomised on a 1:1 basis to receive either bicalutamide 150 mg or placebo once daily. Randomised treatment continued until disease progression. Patients were assessed every 12 weeks for primary tumour, distant metastases, clinical symptoms and PSA levels. The primary endpoints were PFS and OS. The second analysis of the EPC programme with 5.4 year follow-up demonstrated a significant reduction in PFS in patients receiving bicalutamide [10]. Consequently, the independent data and safety committee along with the trial steering committee recommended that randomised trial therapy should be stopped. Investigators and patients should be informed of the findings, and that the treatment code should be broken. The investigators could at their discretion continue patients on open-label bicalutamide, switch to alternative therapy or receive no further therapy.

2.2. Present study update

Between 2012 and 2014 the study was updated for survival status. In all of the 188 men who had died since the last update, the date and cause of death (PCa or other cause mortality) were recorded. Updated survival information could not be retrieved in 154 (28.6%) of the 538 patients alive at the last data lock 30th August 2008 [6]. The 154 patients were therefore censured on that date. Retroactively, body mass index (BMI) and Charlson co-morbidity index at entry were calculated based on baseline physical examination, medical history and concurrent medication. The dataset was locked 1st February 2014. The median follow-up of patients alive was 14.6 (10.2–18.3) years.

2.3. Statistical analysis

Continuous data are presented as median with range unless indicated otherwise. Chi-square test was used to test for independence. Kaplan–Meier analysis was used to estimate OS and competing risk analysis was used