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Original Research

Higher sexual interest with androgen receptor inhibitor monotherapy than with castration plus an androgen receptor inhibitor in prostate cancer patients treated with curative radiotherapy, but otherwise small health-related quality of life differences: A randomised prospective 18-month follow-up study

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Abstract ***Purpose:*** To prospectively study differences in health-related quality of life (HRQoL) in patients with localised/locally advanced prostate cancer (PC) treated with curative intended radiation therapy and randomised to androgen receptor inhibitor monotherapy treatment versus castration plus an androgen receptor inhibitor used continuously. Time to Prostate Specific Antigen (PSA) relapse, time to symptomatic metastasis and overall survival (OS) were also described for the two groups.

Patients and methods: From 2005 to 2011, a total of 110 patients were randomised at a ratio of 1:1. HRQoL was assessed at six time points: before randomisation, before radiotherapy (RT) start and 9, 12, 15 and 18 months after randomisation, using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and EORTC QLQ-PR25.

Results: At the 3-month follow-up, statistically significant differences between the two groups were found for overall quality of life ($p = 0.006$), fatigue ($p = 0.023$), sexual interest

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($p < 0.001$) and urinary problems ($p = 0.036$). Small clinical differences were noted for overall quality of life, role functioning, fatigue, pain, sleeping problems and urinary problems. At that assessment point, clinical differences between the groups were substantial regarding sexual interest and moderate regarding sexual functioning (the latter indicated only by patients reporting having sexual interest at baseline). All statistical and clinical differences favoured the androgen receptor inhibitor monotherapy arm. At 18 months after randomisation, statistically significant differences were found for cognitive functioning ($p = 0.040$) and sexual interest ($p = 0.011$), both favouring the androgen receptor inhibitor monotherapy arm.

Conclusion: The results suggest that neo-adjuvant androgen receptor inhibitor monotherapy might be preferred compared to castration plus an androgen receptor inhibitor before curative intended RT in men with localised/locally advanced PC, with higher levels of HRQoL, especially concerning sexual interest. HRQoL differences over time were small. The observation time and study sample were too small for evaluating time to PSA progression and OS. Further studies are needed to confirm the results. The study was registered in, identification number NCT02382094.

1. Introduction

Androgens play a prominent role in the development, maintenance and progression of prostate cancer (PC). The introduction of androgen deprivation therapies (ADTs) in the PC treatment paradigm has resulted in numerous positive effects ranging from a survival advantage for patients with clinically localised or locally advanced disease, to improved symptom control for those with advanced disease [1]. A treatment approach often used in localised/locally advanced PC is combining ADT with curative-intent radiotherapy (RT). The use of gonadotropin-releasing hormone (GnRH) analogue combined with non-steroidal androgen receptor blockade in a neo-adjuvant setting is currently used as standard treatment. PC patients suffer greatly from ADT, such as reduced physical energy and sexual function, in addition to more impotency in PC patients given ADT than in those receiving no therapy [2,3]. Neo-adjuvant ADT before RT has been shown to be effective in PC but negative impact on health-related quality of life (HRQoL), particularly sexuality has been observed [4–6]. Dorff *et al.* [7] noted improved survival when adding ADT to radiation for treatment of localised PC. Concerns over metabolic complications, including cardiovascular morbidity, have raised questions about the level of ADT necessary to improve outcomes, especially considering that escalated radiation doses are utilised. A study performed by the EORTC compared RT with concomitant and adjuvant hormone therapy for 3 years with RT alone in locally advanced/metastatic PC. At 5 years, a survival benefit was found in the combination arm (78% versus 62%; $p = 0.001$) [8].

Castration plus an androgen receptor inhibitor used continuously in neo-adjuvant settings is one of the treatment options, but many clinicians appeared to have instead used androgen receptor inhibitor monotherapy in attempts to minimise the side-effects related to sexual interest and function. In Sweden, both regimens are used for 2–6 months. There is an on-going discussion concerning HRQoL, if reduced volumes reflect reduced targets of irradiation, and about the need for ADTs in an era of high dose irradiation.

The present randomised trial was conducted to compare androgen receptor inhibitor monotherapy (Experimental arm) and castration plus an androgen receptor inhibitor used continuously (Standard arm) regarding differences in HRQoL at six time points: at inclusion before ADT, before start of RT (3 months after randomisation) and 9, 12, 15 and 18 months after randomisation. Time to PSA relapse, time to disease progression and overall survival (OS) were recorded as exploratory variables.

2. Patients and methods

2.1. Patients

Patients subjected for curative intended RT due to localised/locally advanced PC during 2005–2011 were eligible for this randomised controlled trial. Inclusion criteria were histopathological PC; patients referred for curative intended radiation therapy with mainly intermediate risk, and also low-risk patients were included if they were given neo-adjuvant therapy, relapse free 5 years after diagnosis of other malignancies and capable of complying with study requirements and consenting to participate. Patients with basal cell carcinoma were eligible. Exclusion criteria were as follows: distant metastasis, myocardial infarction within the last 6 months, severe atherosclerosis, inflammatory bowel disease, urinary incontinence, severe hepatic failure with serum bilirubin or Aspartate Aminotransferase (AST)/Alanine Aminotrasferase (ALT) >2.5 times maximum normal reference limit and serum creatinine > 225 mmol/l. Concurrent participations in other clinical trials were not allowed. A research nurse