ELSEVIER

Urologic Oncology: Seminars and Original Investigations 31 (2013) 549–556

UROLOGIC ONCOLOGY

Original article

# Continuous vs. intermittent androgen deprivation therapy for metastatic prostate cancer

Johan F. Langenhuijsen, M.D.[a,*], Dirk Badhauser, M.S.[b], Berthold Schaaf, M.S.[c], Lambertus A. L. M. Kiemeney, Ph.D.[a], J. Alfred Witjes, M.D., Ph.D.[a], Peter F. A. Mulders, M.D., Ph.D.[a]

[a] *Department of Urology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands*
[b] *Medical Department, Sanofi-Aventis, Berlin, Germany*
[c] *Factum Statistics, Offenbach/Main, Germany*

Received 3 January 2011; received in revised form 20 February 2011; accepted 15 March 2011

**Abstract**

**Objectives:** To analyze the predictive value of PSA for progression and the role of testosterone for quality of life (QOL) in patients with androgen deprivation therapy (ADT) for metastatic prostate cancer.

**Materials and methods:** PSA and testosterone data were used from a phase III trial randomizing patients without progression and PSA $<$ 4 ng/ml ($n$ = 193), after 6 months induction course, between continuous (CAD) ($n$ = 96) and intermittent (IAD) ($n$ = 97) ADT. The 2-year risk of progression was calculated for baseline PSA, 'fast' and 'slow' PSA decline to $<$ 4 ng/ml (60 days cut-off), PSA nadir, performance status and pain. Testosterone kinetics and QOL were also evaluated. Univariate Kaplan Meier survival analysis and log rank tests were used to compare the risk of progression.

**Results:** For progression analysis, 173 patients' data were available. The 2-year risk of progression for baseline PSA $<$ 50 ng/ml, 50 to $<$500 ng/ml, and $\geq$500 ng/ml was 25%, 55%, and 76% ($P$ = 0.03) in CAD, and 38%, 64%, and 85% ($P$ = 0.006) in IAD, respectively. The 2-year risk of progression for PSA nadir $\leq$ 0.2 ng/ml, and $>$ 0.2 to 4 ng/ml in CAD was 31% and 70% ($P < 0.001$), respectively. In the IAD group, a similar trend was seen. Patients with PSA nadir $\leq$ 0.2 ng/ml, though had significantly higher 2-year risk of progression compared to CAD (53% vs. 31% ($P$ = 0.03), respectively. PSA decline showed no predictive value. Patients without pain had a significantly lower 2-year risk of progression in both groups. Without ADT testosterone remained at castrate level for 4 months. After the first and second IAD cycle 92% and 46%, respectively, had a normalized testosterone. No QOL difference was found, although more side effects occurred in CAD.

**Conclusions:** Metastatic prostate cancer patients with high baseline PSA, pain, and high PSA nadir have a poor prognosis with ADT. Patients with low PSA nadir do significantly worse with IAD compared with CAD. Low testosterone after ADT and incomplete testosterone recovery may explain similar QOL. Therefore, IAD is not a good treatment option for many metastatic prostate cancer patients. 

*Keywords:* Intermittent androgen deprivation; Prostate cancer; Testosterone; Prostate specific antigen

## 1. Introduction

The standard treatment for metastatic prostate cancer is androgen deprivation therapy (ADT) with a symptomatic and/or objective response in approximately 80% of patients [1]. Because many patients are on ADT for several years, the toxicity plays an important role. The treatment is associated with several side effects, including hot flushes, loss of libido, erectile dysfunction, cognitive dysfunction, fatigue, depression, osteoporosis, gynaecomastia, anaemia, loss of muscle mass, and metabolic syndrome with an increased cardiovascular risk [2–4]. The concept of intermittent androgen deprivation therapy (IAD) has been developed in preclinical studies aiming at the delay of the castrate resistant state [5,6]. Another goal was the reduction of toxicity, during the off-treatment phase, and improvement of quality of life (QOL), which was shown for the first time in early clinical studies and was ascribed to the recovery of serum

* Corresponding author. Tel.: +31-24-361-3735; fax: +31-24-354-1031.

*E-mail address:* h.langenhuijsen@uro.umcn.nl (J.F. Langenhuijsen).

1078-1439/$ – see front matter 
doi:10.1016/j.urolonc.2011.03.008

testosterone levels [7,8]. However, these results were preliminary and patient numbers were small. Indeed, the exact relation of changing testosterone levels during IAD and QOL has been discussed in few reports so far. The remaining question is whether it is possible to identify a subgroup of patients, based on certain disease characteristics, which could benefit from IAD. Since a recent study has shown that the PSA response on ADT is a strong predictor of survival [9], our hypothesis is that PSA may also facilitate to identify patients that are suitable for IAD. The goals of this study are to analyze the predictive value of PSA levels for progression and the role of testosterone kinetics on QOL in patients with metastatic prostate cancer during continuous or intermittent hormonal treatment. Further, the influence of baseline performance status (PS) and pain on progression is assessed.

## 2. Patients and methods

### 2.1. Study design

The data from the Therapy Upgrading Life in Prostate cancer (TULP) study are used for this analysis. The TULP study is a multicenter, open, randomized controlled trial in which 43 centers from 12 countries have participated. The study has been approved by an Independent Ethics Committee and the Institutional Review Boards of participating clinics. A written informed consent of each patient has been obtained. All patients who already had received hormonal treatment for prostate cancer or had a neoplasm other than non-melanoma skin cancer were excluded. Other exclusion criteria were hepatic or renal dysfunction and the use of medication interfering with the interpretation of therapy results. Previous radiation therapy or surgery of the prostate was allowed. The primary objective of the original study was to determine whether time to clinical progression during IAD is equivalent to time to clinical progression during continuous androgen deprivation (CAD) in metastatic prostate cancer patients. Secondary objectives were to determine QOL, side effects, and overall survival.

Patients were included between January 1998 and September 2001 and the median follow-up from randomization was 31 months (range 0.8–47 months). Eligible patients had histologically proven prostate cancer with positive lymph nodes or distant metastases (T2-4N1-3M0 or T2-4NxM1), an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and a general life-expectancy of at least 18 months. A total of 290 patients were enrolled and received the study medication.

Patients were treated for a 6-month induction course of maximal androgen blockade (MAB) consisting of buserelin 6.6 mg (Suprefact), a 2-monthly subcutaneous depot, and oral nilutamide 300 mg (Anandron) (once a day for the first 4 weeks and 150 mg daily thereafter). At the end of the induction course, patients without clinical progression and a PSA level $< 4$ ng/ml ($n = 193$) were centrally randomized between CAD ($n = 96$) and IAD ($n = 97$). Non-responding patients ($n = 97$), who either failed to achieve or maintain PSA $< 4$ ng/ml during the induction course or had clinical progression, were excluded from the study protocol and were not followed for survival. These patients were treated off-study according to the treating physician's choice. At the time of study design (mid-1990s), there was little experience with IAD. The rationale for randomizing patients who reached a PSA threshold $< 4$ ng/ml was empirical and based on preliminary reported data. Also, the moment of reinstitution of androgen deprivation during off-therapy intervals when a PSA rise $\geq 10$ ng/ml (M0 disease at baseline) or $\geq 20$ ng/ml (M1 disease at baseline) occurred, was chosen on the basis of available data. In patients randomized for IAD, the ADT was discontinued and reinstituted when PSA reached the aforementioned values. Each subsequent IAD cycle consisted of a variable period of MAB, until PSA level reached $< 4$ ng/ml again, and an off-treatment phase. In both randomization groups, MAB was administered continuously once clinical progression occurred. Patients were provided with medication during the study protocol, consisting of a maximum of three cycles of IAD. Clinical progression was assessed according to the European Organization for Research and Treatment of Cancer (EORTC) criteria used in the 1990s (Table 1) [10]. PS was scored at months 2, 4, 5, and 6, and 2-monthly after randomization. Clinical evaluation for tumor stage or progression was performed at randomization and 6-monthly thereafter or as clinically indicated until the end of the study. Tumor dimension assessment was performed by digital rectal examination or transrectal ultrasonography and radiological evaluation by bone scan, chest X-ray, ultrasonography or computerized tomography of the abdomen. QOL assessment was done with the EORTC general health related quality of life questionnaire (EORTC QLQ-C30-version 2.0). Also a validated disease specific questionnaire (EORTC module for prostate cancer, QLQ-PR24) was used. Every six months, plus at month 8, patients filled out these questionnaires. Laboratory tests were performed 2-monthly at an independent central laboratory (Bio-Inova Life Sciences International, Plaisir, France) and contained a hematologic and chemistry profile, including PSA and testosterone values. The post-study analysis of PSA and testosterone values in 2010 has been performed by an independent biostatistician (B.S.) at Factum Statistics (Offenbach/Main, Germany).

Table 1
EORTC criteria (1989) for clinical progression in prostate cancer

| | |
|---|---|
| Progression | Any lesion increases in size or any new lesion appears, regardless of what the response of the other lesions has been |
| | Increase in any measurable deposit by more than 25% |
| | Increase in volume of primary tumor by more than 50% |
| | Significant deterioration in symptoms, decrease in weight, or decrease in performance status |
| | Increase in acid or alkaline phosphatase alone is not to be considered an indication of progression |