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Health-Related Quality of Life in 536 Long-Term Prostate Cancer Survivors after Treatment with Leuprorelin Acetate: A Combined Retrospective and Prospective Analysis

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Keywords
Prostate cancer · Androgen-deprivation therapy · Leuprorelin acetate · Health-related quality of life

Abstract
Introduction: We investigated the health-related quality of life (HRQoL) of long-term prostate cancer patients who received leuprorelin acetate in microcapsules (LAM) for androgen-deprivation therapy (ADT). ***Methods:*** The observational study was carried out by 30 office-based German urologists in 536 prostate cancer (PCa) patients treated for ≥5 years with LAM and in 116 patients of an age-matched control group (CG). Data on HRQoL and health status was collected prospectively using validated questionnaires QLQ-C30, QLQ-PR25 and Karnofsky Index. Data on effectiveness (clinical response, prostate specific antigen [PSA], testosterone) and safety was collected retrospectively from patients' health records. We used descriptive statistics to analyze the data. ***Results:*** The mean treatment duration was 8.6 years (range 4.5–19.8 years). General health status (QLQ-C30) was comparable for both groups. Differences were observed regarding physical – and role functioning. ADT patients rated single items slightly worse than CG. Karnofsky-Index showed comparable high values (median of 90%). QLQ-PR25 revealed more PCa-related symptoms for ADT patients. Within 6 months, median PSA level declined >90% and median testosterone levels declined below castration level from 4.0 to 0.2 ng/mL. Clinical response (European Organisation for Research and Treatment of Cancer criteria) was observed in at least 90% of ADT patients. ***Conclusions:*** Long-term ADT with LAM is a well-accepted, tolerated, effective, and low-burden treatment option for patients with advanced, hormone-sensitive PCa.

Introduction

Prostate cancer (PCa) is the most prevalent cancer and the third-leading cause of cancer-related death in men, with an estimated 60,000 new cases and 13,000 deaths annually in Germany [1]. With a mean age for disease onset of 71 years, PCa is typically identified as an "old man's" disease. The difference between disease incidence and mortality is currently rising since the age-standardized

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mortality rate was decreasing during the last 20 years. On the other hand, an increase in early disease stages was observed, most likely due to the constantly increasing use of the prostate-specific antigen (PSA) for early detection [2].

Treatment of PCa has improved over the last decades to an extent that in a majority of patients in an early stage, PCa can be considered a curable disease; in a recurrent and advanced or metastatic stage, PCa can be considered a long-term surviving disease. Among the initial therapeutic regimens, androgen-deprivation therapy (ADT) has been the preferred treatment in advanced PCa for 70 years [3, 4]. Recent therapeutic options, such as CYP17 inhibitors or novel androgen-receptor blockers in pre- or post-chemo setting as well as a combined chemo-hormone therapy in the subgroup of hormone-sensitive, newly diagnosed, metastatic PCa essentially use ADT as backbone-therapy [2]. In order to achieve androgen deprivation, surgical or medical castration and the use of antiandrogens were the 2 methods of choice [5].

Since the beginning of the 1990s, LHRH agonists, the predominant form of medical ADT, have been used to treat advanced and hormone-sensitive PCa [5]. LHRH agonists decrease testosterone levels to the castration limit within 3–4 weeks after a short initial increase known as "flare-up" effect [6–8]. A good tumor control with sufficient response rates and patients' treatment acceptance mainly depends on the functional well-being and issues of health-related quality of life (HRQoL) among the constantly rising sample of long-term PCa survivors.

Thus, in our study on HRQoL we investigated leuprorelin acetate in microcapsules (LAM), an established LHRH agonist used as first-line treatment in advanced PCa [9, 10]. LAM is the most widely prescribed ADT in Germany, is marketed since 1991, and is therefore well suited to assess the status of long-term ADT survivors. However, relatively little is known about such survivors and neither HRQoL nor the maximum time period during which the tumor can be controlled using ADT has been shown in an office-based setting reflecting daily practice.

Methods

Design

This non-interventional study was performed as a combined retrospective and prospective long-term data collection in accordance with the German drug law §67 section 6. The study provided data collected prospectively during the individual last (i.e., current) visit of each considered patient including demographics, HRQoL-questionnaires, and therapeutic contentment as well as retrospectively concerning the historic development of efficacy and safety variables. Data collection started on August 15, 2011 and ended on October 9, 2012, covering a documentation period between June 10, 1992 and June 11, 2012. The study is registered in the study registry of the German Association of Research-based Pharmaceutical Companies (vfA) under the unique Study No.: ENA E005/DE-N-LEU-019.

Patients and Sites

Data of 536 patients from 30 German urologic sites with advanced and hormone-sensitive PCa was collected after ADT with subcutaneous LAM for at least 5 years of therapy. In addition, data of 116 cancer- and ADT-free age-matched urological patients (age ≥77 years) served as controls. Patient selection was at the discretion of the treating physician. Each site provided data records for 8–20 PCa patients and for up to 4 patients of the control group (CG).

Data Collection

Data was collected and processed under strictly pseudonymous conditions. Tumor-related data such as clinical response, PSA, and testosterone levels were collected retrospectively over 6-month time intervals only for PCa patients (n = 536). Baseline demographics with Karnofsky Index and the HRQoL data was documented for both the PCa patients (n = 536) and the CG (n = 116) at the current (prospective) visit. In order to achieve robust HRQoL data, we used the standardized and validated European Organisation for Research and Treatment of Cancer quality-of-life questionnaire QLQ-C30 and the disease specific questionnaire module QLQ-PR25 [11].

In these questionnaires, related questions were to be answered on 4 possibilities or on a visual analogue scale from 1 to 7. For evaluation, the questions were summarized in groups to calculate sum scores for the different sub-scales. These sub-scores were then to be transformed mathematically into final results between 0 and 100, presenting 100 as the best value for all functional scores und as the worst result for all symptom scores.

Statistics

Data of all patients was analyzed using descriptive statistics in an exploratory manner. Missing data was marked as such. Safety was evaluated according to the number and severity of adverse events and adverse drug reactions based on MedDRA terminology version 15.0.

Ethical Principles

The study was conducted in accordance with the Declaration of Helsinki and announced at the Federal Institute for Drugs and Medical Devices (BfArM), the National Association of Statutory Health Insurance Physicians (KBV), and the National Association of Statutory Health Insurance Funds (GKV Spitzenverband). All patients provided a signed written informed consent.

Results

Baseline Characteristics

The initially treated study set consisted of 540 patients diagnosed with PCa. Since treatment duration of 4 (0.7%) patients was below 5 years of treatment, they were not

Table 1. Demographic characteristics

Parameter*	LAM therapy (n = 536)	Control group (n = 116)
Age, years	79.6±6.3 (80.0; n = 536)	80.5±3.1 (80.0; n = 116)
Height, cm	174.2±6.3 (174; n = 476)	174.7±5.6 (174.0; n = 115)
Weight, kg	83.1±12.6 (82.0; n = 472)	82.2±10.6 (81.0; n = 112)
BMI, kg/m^2	27.3±3.7 (26.8; n = 472)	26.9±3.1 (26.5; n = 111)
Karnofsky-index, %	88.0±12.7 (90.0; n = 522)	88.4±12.0 (90.0; n = 114)

* Mean ± SD; values in brackets denotes median and individual case number.

considered for evaluation. Thus, HRQoL, effectiveness, acceptance, safety and local tolerability were recorded for the remaining 536 patients treated with LAM for at least 5 years. For the separately recruited age-matched CG, a sample of 116 cancer- and ADT-free patients was considered.

Baseline demographics was recorded at the current visit for both the PCa patients and the CG without relevant differences between the 2 patient sets. Mean age ± SD (79.6 ± 6.3 vs. 80.5 ± 3.1 years), height, weight, and BMI were comparable between the 2 patient sets as was the Karnofsky-Index (88.0 ± 12.7 vs. 88.4 ± 12.0; Table 1).

The age of the PCa patients ranged between 48 and 98 years, with the largest group being in the age range 71 to 85 years (n = 463, 71.6%). Most of the 536 treated PCa patients received therapy with LAM as monotherapy (322/60.1%), followed by combinations with antiandrogens (bicalutamide, flutamide, cyproteron acetate; 163/30.4%), combination with radiation (27/5.0%) and combinations with others (24/4.5%). Moreover, LAM treatment was recognized as first-line therapy in 349 patients (65.1%), after radical prostatectomy (RP) in 163 patients (30.4%), and after radiation therapy in 75 patients (14.0%; multiple remarks possible). The time between diagnosis of PCa and the onset of LAM therapy did not exceed 1 month for about half of the 536 PCa patients (median 1.0). Before start of LAM therapy, 333 out of 536 PCa patients (62.1%) were found to be with comorbidities such as hypertension (36.4%), coronary heart disease (17.5%), benign prostatic hyperplasia (15.1%), diabetes (11.2%) and cardiac insufficiency (7.5%; again multiple remarks possible). The mean total duration of treatment with LAM in this study was 8.6 years (SD 2.9, median: 8.0, maximum 19.8 years), resulting in a total of 4,610 patient treatment-years. The categorized duration of LAM therapy during the study period is displayed in Table 2.

Table 2. Duration of LAM therapy

Categories of treatment duration in years	Patients overall (n = 536), n (%)
≥5 until <6 years	120 (22.4)
At least 6 until <7 years	90 (16.8)
At least 7 until <9 years	114 (21.3)
At least 9 until <10 years	39 (7.3)
At least 10 until <12 years	101 (18.8)
≥12 years*	72 (13.4)

* Maximum duration of LAM therapy was 19.8 years.

Health-Related Quality of Life

Assessment of the general health status according to QLQ-C30 revealed a mean of 64.6 ± 20.5 (median: 66.7) for LAM-treated patients versus 66.8 ± 20.3 (median: 66.7) for the age-matched CG (p = 0.3117; 100 = best; Fig. 1a). This trend with comparable results between CG and PCa patients can be observed for the QLQ-C30 functional scores (100 = best) and most of the symptom scores (100 = poor). Marginal differences were seen for physical functioning (73.2 ± 23.1 PCa vs. 78.1 ± 21.0 control; p = 0.0402) and role functioning (70.6 ± 30.4 vs. 74.4 ± 25.7; p = 0.1648; Fig. 1a). The symptoms fatigue (33.6 ± 25.1 vs. 28.8± 23.3; p = 0.0629), dyspnoea (24.0 ± 28.5 vs. 19.6 ± 26.9; p = 0.1307) and insomnia (28.9 ± 32.6 vs. 23.7 ± 27.2; p = 0.0751) were also assessed to be slightly inferior in PCa patients (Fig. 1b).

Evaluation of the prostate-specific QLQ-PR25 showed a worse status regarding sexual activity (12.0 ± 20.6 vs. 23.7 ± 25.7; p < 0.0001) and sexual functioning (43.3 ± 25.8 vs. 55.9 ± 27.0; p = 0.0067) for PCa patients (100 = best; Fig. 1c). Results of the QLQ-PR25 symptom scores (100 = poor; Fig. 1d) displayed that PCa patients had slightly less urinary symptoms (28.2 ± 19.8 vs. 31.2 ± 19.2; p = 0.1472). Symptoms of androgen suppression were clearly more pronounced in PCa patients (21.4 ± 17.3 vs.

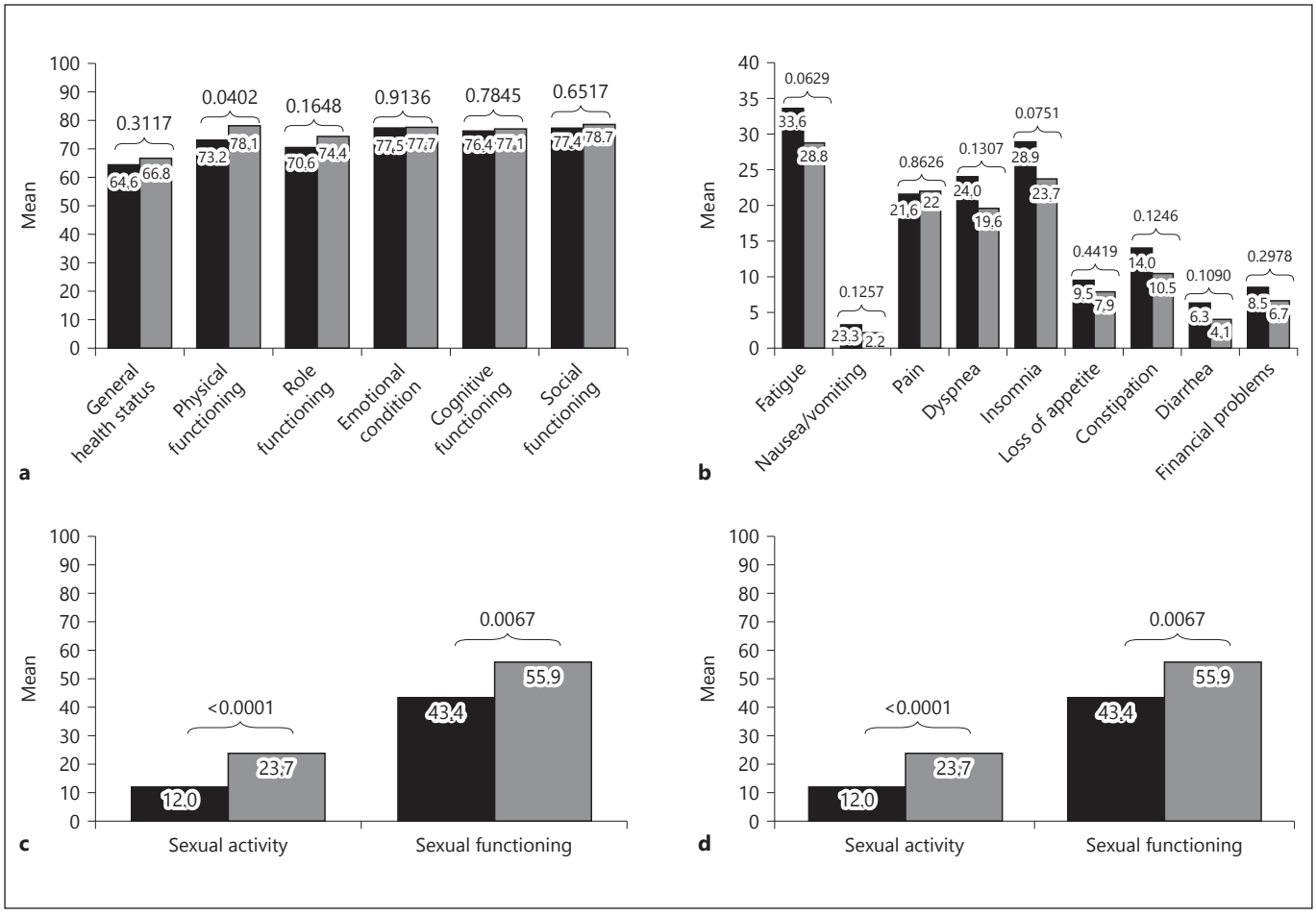

Fig. 1. a–d Overall results of quality of life assessment by European Organisation for Research and Treatment of Cancer Questionnaires QLQ-C30 and QLQ-PR25. The Quality of Life Questionnaire categorized answers between 1 and 4 or 1 and 7 (1 = no symptom) were transformed according to the QLQ scoring manuals into values between 0 (= no symptom) and 100. One hundred is defined as the best result for functional scores and the worst result for symptom scores.

10.8 ± 13.2; $p < 0.0001$), and PCa patients also had a higher need of incontinence assistance (29.6 ± 34.2 vs. 16.7 ± 20.5; $p = 0.0056$). However, 163 of the 536 PCa patients had previously undergone RP.

Continuously high values were reported in a majority of patients for the Karnofsky-Index (median of 90% for both PCa patients and the CG; Table 1). With an Index of ≥70% in about 80% of PCa patients and patients of the CG, the overall patients' performance status therefore indicated a long-term clinically stable condition.

In addition, constantly high ratings of "excellent" and "good" in at least more than 95% of the PCa patients were observed for the physicians' assessments of treatment regimen, tolerability of LAM treatment, and handling of the used syringe.

Effectiveness

The clinical response to LAM therapy as assessed by the treating physician using an overall clinical rating supported by investigational and laboratory results (e.g., TRUS, DRE, PSA, testosterone) could be documented in at least about 90% of the PCa patients during a treatment period of up to about 20 years (resulting mean of 8.6 years, median of 8.0 years, and maximum of 19.8 years).

In general, the clinical response (i.e., either stable disease or partial/complete remission) remained high during the entire observation period with still over 90% at the current visit.

Median PSA levels decreased by >90% within the first 6 months after start of LAM therapy (from 8.1 to 0.4 ng/mL) and stayed below this level for up to 13 years. The median PSA value at the current visit was still

Table 3. Adverse events and adverse drug reactions

	LAM therapy (n = 536), n (%)
Patients with AEs	96 (17.9)
Patients with SAEs	11 (2.1)
Patients with AEs, not classified as ADRs	44 (8.2)
Patients with ADRs	64 (11.9)
Mild	26 (4.9)
Moderate	34 (6.3)
Severe	4 (0.7)

AE, adverse event; SAE, serious adverse event; ADR, adverse drug reaction.

0.3 ng/mL. Also, well within the first 6 months of therapy, median testosterone levels were suppressed from 4.0 to 0.2 ng/mL and were therefore below the castration level of <0.5 ng/mL. During 13 years of therapy, the median testosterone levels remained constantly below the castration level with a median value of 0.15 ng/mL in year 13 and at the current visit.

Safety and Tolerability

Adverse events occurred in 96 (17.9%) of the 536 treated PCa patients, with adverse drug reactions (ADRs) in 64 (11.9%) of these patients (i.e., 0.014 ADRs per treatment year) and hot flushes as the most frequently reported ADRs. Serious adverse events (SAEs) were recorded in 11 (2.1%) of the patients (mainly hot flushes and hyperhidrosis). The detailed numbers of patients with adverse events, SAEs, and ADRs are provided in Table 3. During the time of treatment observation, no relevant abnormalities were observed regarding lab results with hemoglobin, creatinine, HbA_{1c}, glucose, GOT, GPT, γ-GT, LDH, cholesterol, HDL and AP.

Discussion

The present observational study can be categorized as one of few studies investigating ADT over a very long period of time providing treatment durations of up to about 20 years. At the end of this observational period, results on HRQoL and Karnofsky-Index were collected as a special feature at one current, prospective visit from 536 PCa patients and were compared with an age-matched CG of 116 cancer- and ADT-free urological patients. In general, what is most important for treatment success in long-term therapies is the tolerability of medication and acceptance of therapy. Thus, the collection of data on HRQoL will have a great influence on the additional assessment of possible therapeutic regimens. For the choice of appropriate treatment options not only the course of effectiveness-related variables like tumor remission, PSA, and testosterone levels have to be considered but also the different aspects of HRQoL, in particular, the known and partially very demanding complications of an advanced PCa therapy such as sexual, urological and intestinal dysfunctions [5, 10, 12–15]. A limitation of this study is the retrospective data collection of data on efficacy, safety and tolerability during the long-term treatment phase for the PCa patients.

Regarding the achieved study results, tumor control and overall HRQoL with patients' general physical condition and health status were remarkably well balanced between the PCa patients and the CG, which is in line with previous studies [10, 12]. In addition, single aspects of HRQoL as well as of the Karnofsky-Index in long-term PCa survivors were within the range of the outcome in the CG representing age-matched but cancer-free, urological patients.

However, as also seen in other trials, sexual activity and sexual functioning were clearly more affected in PCa patients receiving long-term ADT [15, 16], thus showing better sexual activity ($p < 0.0001$) and sexual functioning ($p = 0.0067$) in the CG. As expected for the PCa patients due to prior ADT and RP, respectively, the symptom scores "hormonal withdrawal" ($p < 0.0001$) and "incontinence assistance" ($p = 0.0056$) revealed pertinent current results.

Nevertheless, the success of ADT in advanced PCa is also defined by response (complete remission, or partial remission, or stable disease), decrease of PSA levels, and effective testosterone suppression down to the castration limit or below [5, 13]. In respect of these parameters, the present data collection revealed that therapy with LAM in long-term PCa survivors treated for up to a maximum of about 20 years proved effective. In other studies, much shorter ADT treatment durations (most frequently over around 1 year) have been investigated. LAM was investigated in a randomized, open-label European multicentre study with 296 patients over a 12-month period. After 12 months' therapy with the 6-month depot, a median PSA reduction of 89% to 0.3 ng/mL was observed, and median serum testosterone levels were suppressed below 0.2 ng/mL (0.15 ng/mL) [10].

A European Organisation for Research and Treatment of Cancer study investigated whether short-term andro-

gen suppression plus radiation is not inferior to long-term androgen deprivation therapy [14]. After a 5-year follow-up, long-term androgen suppression showed an advantage regarding overall mortality (15.2%) compared to the short-term group (19.0%).

With regard to safety, tolerability and acceptance of the long-term ADT-therapy, the results adequately support previous findings in terms of the known safety profile for LAM with hot flushes as the most frequently reported ADRs and only a small number of ADRs in summary (64/536 patients, 11.9%; 4,610 patient treatment years; i.e., 0.014 ADRs per year). Hot flushes are a common side effect of LHRHa treatment and are reported in a higher proportion of patients in prospective trials [17–20]. In our study, we selected patients receiving at least 5 years of LHRHa treatment. Patients who discontinued treatment due to side effects are not investigated in this cohort. The consistently high values for the Karnofsky-Index and the physicians' assessments of treatment regimen, local tolerability and handling of the syringe also indicated long-term clinically stable conditions for the overall health status of the PCa patients.

Conclusion

The vast majority of the long-term surviving PCa-patients treated with LAM as ADT in this non-interventional data collection provided a very stable general health status that was comparable to current cancer- and ADT-free urological patients. These surprisingly good results were achieved despite the known bias concerning not recorded drop-outs in retrospective trials. This is supported by a constantly high outcome of data on HRQoL and Karnofsky-Index after a therapy with LAM of up to almost 20 years in the PCa patients. In addition, effectiveness results regarding the course of clinical response, testosterone suppression and PSA reduction were as expected during the retrospective treatment period.

In summary, long-term ADT with LAM is a well-accepted, tolerated, effective and low-burden treatment option for patients with advanced, hormone-sensitive PCa.

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Authors Contribution

Both authors declare that they have fulfilled the authorship criteria. Authors were substantially involved in the design of the study and data analysis and interpreted the data. Furthermore, they drafted and revised the manuscript and finally approved the manuscript for submission. Both authors agree being accountable for all aspects of the work.

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