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Six-Month Depot Formulation of an LHRH agonist for the Treatment of Advanced Prostate Cancer – Efficacy and Tolerability

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Abstract

We investigated the efficacy and tolerability of a 6-month depot microcapsule formulation of the LHRH agonist leuprorelin acetate in patients with advanced prostate cancer. A total of 480 patients from 62 office based urologists were enrolled in this non-interventional study (NIS), of whom 471 met inclusion criteria and were evaluable. The patients were followed up for 6 months. Given the variety of prior treatments, the following patient subgroups were considered: newly diagnosed, watchful waiting, radical prostatectomy, radiotherapy, endocrine treatment in general, and LHRH agonist/antagonist treatment in particular. In the present analysis we focused on two of these subgroups: Newly diagnosed patients with no previous endocrine treatment (Group 1, n = 60) and patients previously treated with an LHRH agonist/antagonist (Group 2, n = 277).

Following injection of the 6-month depot of leuprorelin acetate, prostate-specific antigen (PSA) levels among Group 1 patients fell below pretreatment values (median, from 5.8 ng/mL to 0.5 ng/mL), while among Group 2 patients (with a median duration of 30.6 months of prior LHRHa treatment) PSA levels further decreased (median, from 0.7 ng/mL to 0.4 ng/mL). In Group 1, testosterone levels were suppressed from a median of 2.5 ng/mL to 0.12 ng/mL. In the total group with available testosterone data (n = 152), testosterone levels decreased statistically significantly (median, from 0.25 ng/mL to 0.10 ng/mL; p = 0.0001).

Only 6 % of all patients (2 % in Group 1) experienced disease progression as defined by EORTC criteria. As adverse events occured hot flushes (1.46 %) and injection site erythema (1.04 %). Treatment did not result in relevant changes of body weight, body mass index, or laboratory parameters and was well tolerated.

In conclusion, treatment of patients with advanced prostate cancer with a 6-month depot injection of the LHRHa leuprorelin acetate resulted in a significant and clinically meaningful decline in PSA levels. In addition, testosterone concentrations were reliably suppressed to levels clearly below the castration limit. Overall, a high remission rate and good tolerance was seen. Both newly diagnosed patients and those receiving the 6-month depot after previous LHRHa treatment benefited from the depot injection.

Keywords: advanced hormone-sensitive prostate cancer · castration level · EORTC criteria · leuprorelin acetate · LHRH agonist · testosterone level

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1. Introduction

According to an estimate of the Robert Koch Institute, roughly 64000 men are newly diagnosed with prostate cancer in Germany every year. It is thus the most common form of cancer in males. With an annual mortality of approximately 13000, it is the third most frequent cause of death from cancer in men in Germany.[1]

The guidelines of the European Association of Urology recommend hormonal therapy with LHRH agonists as standard systemic therapy for long-term treatment of advanced hormone-sensitive prostate cancer.[2] Continuous treatment with LHRHa leads to the blockade of testosterone synthesis in the testes and has a clinical efficacy comparable to that of orchiectomy.[3] However, drug treatment can avoid the psychological unease often associated with surgery and has the advantage of reversibility.

LHRH agonists are available as 1-month, 2-month, 3-month, and 6-month depot formulations.[4] A 6-month depot formulation not only reduces the number of injections but also diminishes the psychological and physical stress related to injections in this population of mostly elderly patients.[4]

The present study investigated a 6-month depot formulation of leuprorelin acetate in microcapsule form (Sixantone®). The study aimed to assess the efficacy and safety of this formulation in a broad office-based urological setting for the treatment of patients with advanced prostate cancer and various prior treatments.

2. Patients and methods

The study was designed to include patients with advanced prostate cancer who had newly diagnosed disease or had received various previous treatments. A total of 62 office based urology practices, all of them members of the German Quality Assurance Working Group of Office-based Uro-oncologists (IQuO)*, participated in this multicenter, non-interventional, observational study. We planned a sample size of 500 patients with a calculated dropout rate of 20 %. Patients with a diagnosis of advanced, hormone-sensitive prostate cancer were eligible for the study. Urologists were allowed to include all patients suitable for treatment with a 6-month LHRH agonist. Patients could have undergone radical prostatectomy, any type of hormonal treatment and/or radiation therapy. However, patients treated with orchiectomy before the start of the study were excluded. Patients were included in the study at the time of administration of the 6-month LHRH agonist Sixantone® (Takeda GmbH) and were followed for 6 months.

The demographic data and disease characteristics including Gleason score[5] and TNM stage[6] were documented at baseline, while all other parameters such as clinical response according to EORTC criteria[7], Karnofsky Index[8], WHO performance status[9] as well as prostate-specific antigen (PSA) and testosterone levels were evaluated at baseline and at 6 months. The laboratory parameters were determined in local labs and included hemoglobin (Hb), glutamic oxaloacetic transaminase (GOT or aspartate transaminase), glutamate-pyruvate transaminase (GPT or alanine transaminase),

Table 1. LHRHa pretreatment. An individual patient could have received more than one active treatment

Active substance	Brand name	n (%)
Total		**277 (100)**
Buserelin	(Only generic name)	3 (1)
	Profact	35 (13)
Leuprorelin	(Only generic name)	29 (10)
	Enantone	6 (2)
	Trenantone	138 (50)
	Sixantone	30 (11)
	Eligard	21 (8)
	Leuprorelin Hexal/Leuprone	7 (3)
Goserelin	(Only generic name)	1 (< 1)
	Zoladex	30 (11)
Triptorelin	(Only generic name)	-
	Decapeptyl	1 (< 1)
	Pamorelin	3 (1)
	Uropeptyl	1 (< 1)
Degarelix	(Only generic name)	-
	Firmagon	8 (3)
Abarelix	(Only generic name)	-
	Plenaxis	1 (< 1)

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Table 2. TNM stage of patients at the time of first diagnosis of carcinoma of the prostate

T stage, n (%)		N stage, n (%)		M stage, n (%)	
Total	480 (100)	Total	480 (100)	Total	480 (100)
T0	3 (1)	N0	148 (31)	M0	206 (43)
T1a	20 (4)	N1	25 (5)	M1a	15 (3)
T1b	20 (4)	Nx	307 (64)	M1b	12 (2)
T1c	124 (26)			M1c	6 (1)
T2a	48 (10)			Mx	241 (50)
T2b	35 (7)				
T2c	59 (12)				
T3a	47 (10)				
T3b	47 (10)				
T4	38 (8)				
Tx	39 (8)				

gamma-glutamyl transpeptidase (γGT), alkaline phosphatase, and creatinine. Body weight and body mass index (BMI) were also measured. Any adverse event and side effect was recorded at the final visit after 6 months of treatment in the relevant part of the case report form. Serious adverse events were immediately recorded by the contract research organization according to German law. The treating physicians made overall assessments of 6-month depot LHRHa therapy for each individual patient and also assessed the tolerability of treatment.

According to the non-interventional character of the study, we used descriptive statistical analysis using standard calculations and graphical methods to represent the data and their distribution. In the case of additional statistical tests performed between measurements at different time points, between treatment groups or between prognostic subgroups of patients, these (and the corresponding p-values) were not meant to test specific hypotheses but to serve as additional information within the descriptive and possibly hypothesis-generating framework. No formal adjustment for multiplicity was performed. If not specified otherwise, two-sided tests were used for analysis.

Clinical trial registry: The study was registered in the registry for non-interventional studies of the Association of Research-Based Pharmaceutical Companies (vfa), under the unique trial number SIX E002/DE-N-LEU-017 (registration date: October 28, 2009).

3. Results

A total of 480 patients with advanced prostate cancer were enrolled in the study, of whom 471 fulfilled inclusion criteria and were evaluated until the end of follow-up. The patients had either newly diagnosed disease (n = 60, 12 %) or had received various previous treatments including a watchful waiting approach (n = 35, 7 %), radical prostatectomy (n = 91, 19 %), radiotherapy (n = 90, 19 %), or endocrine treatment (any type, n = 348, 72 %; and LHRHa, n = 277, 58 %); multiple therapies were allowed. Leuprorelin acetate was the most frequently used LHRHa, with the 3-month depot formulation Trenantone® being administered to half of the patients (Table 1).

The study participants were on average 76.2 ± 8.5 years old, had a mean height of 174.2 ± 6.2 cm, and a mean body weight of 82.2 ± 12.2 kg. The patients had a median [interquartile range] disease duration of 2.2 years [0.3 – 6.4] and were in different tumor stages (Table 2).

Of the patients for whom histopathological tumor grading was performed (n = 308), 85 % had grade G2 or G3 tumors. Of those for whom the Gleason score was determined (n = 403), 59 % had a Gleason score ≥ 7.

Six months after subcutaneous injection of the depot LHRH agonist, the patients with newly diagnosed prostate cancer and no previous treatment (Group 1; n = 60, 12 %) had distinctly lower median PSA levels (median [interquartile range] 0.5 ng/mL [0.1 – 2.3]) as compared to baseline (5.8 ng/mL [1.6 – 19.8]). However, even among the patients of Group 2 (n = 277, 58 %) who had previously received LHRHa therapy for a median duration of 30.6 months [8.9 – 69.2], the PSA levels continued to decrease during treatment with the 6-month depot LHRH agonist, from a median of 0.7 ng/mL [0.1 – 2.7] at baseline to a median value of 0.4 ng/mL [0 – 1.9]. These results provide further evidence for the efficacy of the 6-month depot LHRH agonist (Figure 1). In the total patient population

(n = 471), the decrease in PSA values from a median of 1.3 ng/mL [0.1 – 6.1] to 0.4 ng/mL [0.1 – 1.7] was statistically highly significant ($p < 0.0001$).

Whereas PSA values were determined in all patients, testosterone concentrations were available for only 152 patients (baseline and end of study). In newly diagnosed patients (n = 19, 4 %), the 6-month depot LHRH agonist reduced the testosterone levels from a median of 2.5 ng/mL [0.4 – 4.1] at baseline to 0.12 ng/mL [0.1 – 0.2] at the final visit. Based on the total available sample (n = 152), the testosterone levels decreased from a median baseline value of 0.25 ng/mL [0.1 – 1.9] to a median final value of 0.10 ng/mL [0 – 0.2], which was highly statistically significant ($p < 0.0001$). The desired castration limit (serum testosterone level < 0.5 ng/mL) was thus achieved with the 6-month depot injection of the LHRH agonist in 94 % of the patients at 6 months.

At the end of the 6-month observation period, only 6 % of the patients showed progressive disease as defined by EORTC criteria (Figure 2). In the subgroup of newly diagnosed patients, only 2 % were found to have progressive disease. This high rate of freedom from progression according to EORTC criteria (complete/partial remission or stable disease) reflects the high clinical efficacy of the 6-month depot LHRH agonist therapy.

At the end of the observation period, the evaluation of WHO performance status (n = 464) and Karnofsky Index (n = 471) showed a WHO performance status of 0 or 1 in 74 % of the patients (75 % at baseline) and a Karnofsky Index of 80 % to 100 % in 68 % of the patients (70 % at baseline). In newly diagnosed patients a WHO performance status of 0 or 1 was seen in 88 % of the patients at the end of the observation period (85 % at baseline); and a Karnofsky Index of 80 – 100 % in 84 % of the patients (83 % at baseline).

Treatment with the 6-month depot LHRH agonist did not result in relevant changes of body weight or BMI (baseline: 27.1 ± 3.6 kg/m^2; 6 months: 27.1 ± 4.2 kg/m^2) or in any of the laboratory parameters determined (Hb, GOT, GPT, γGT, alkaline phosphatase, or creatinine) and was generally well tolerated. The only adverse event that occurred in more than 1 % of patients were hot flushes (1.46 %) and erythema at the site of the injection (1.04 %).

The treating physicians' overall assessments of the 6-month depot LHRH agonist therapy for the individual patients were "very good" or "good" for 86 % (n = 404) of the patients. Further, 6-month depot therapy was considered to be "very well" or "well" tolerated in 95 % of the patients (n = 445) (Figure 3).

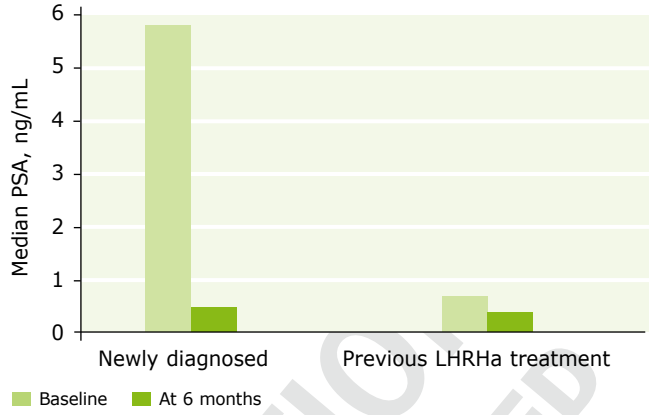

Figure 1. Decrease in PSA levels during treatment with a 6-month depot formulation of leuprorelin acetate in microcapsules in newly diagnosed, previously untreated patients (Group 1; n = 60, 12 %) and patients previously treated with an LHRHa (Group 2; n = 277, 58 %).

4. Discussion

Former studies have demonstrated comparable efficacy and safety profiles of 1, 3, and 6-month depot formulations of leuprorelin acetate in microcapsules.[4,10]

Tunn et al.[4] reported a response rate of 85 % according to EORTC criteria in prostate cancer patients after 12 months of treatment with a 6-month depot formulation of leuprorelin acetate. In the present study, the progression rate according to EORTC criteria at 6 months was only 6 %.

Furthermore, Tunn et al[4] found a testosterone response to levels below the castration limit in 98 % of patients after 12 months, and the median PSA level was 1.1 ng/mL. In the present non-interventional study, a comparable proportion, i.e., 94 % of the patients, showed testosterone levels below the castration limit after 6 months, with a median PSA level as low as 0.4 ng/mL.

The median age of the present study cohort was somewhat higher (76.2 years) than that of the cohort studied by Tunn et al. (73.6 years)[4], and only 12 % of our patients had newly diagnosed disease compared with 85.8 % in Tunn et al.'s cohort. These differences may explain the poorer WHO performance status observed in our study in which 74 % of all patients had a performance status of 0 or 1 as compared to 91.6 % of the patients in the study by Tunn et al.. In the subgroup of newly diagnosed patients in our study, 88% had a performance status of 0 or 1, which is comparable to the proportion of patients with this performance status in the cohort studied by Tunn et al..

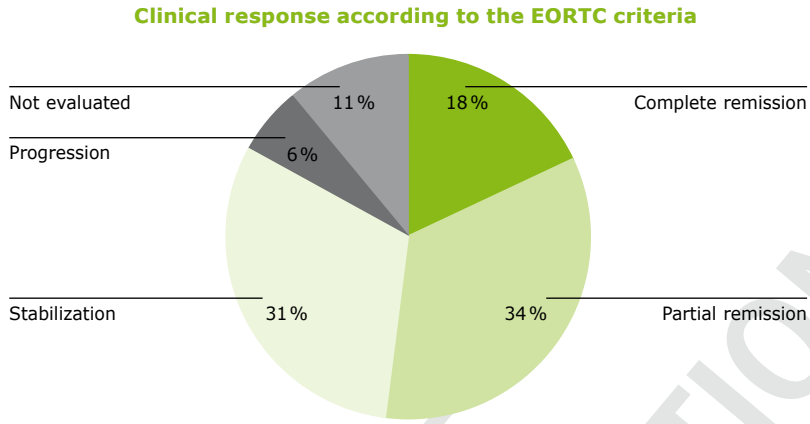

Figure 2. Tumor status following the administration of 6-month depot LHRH agonist

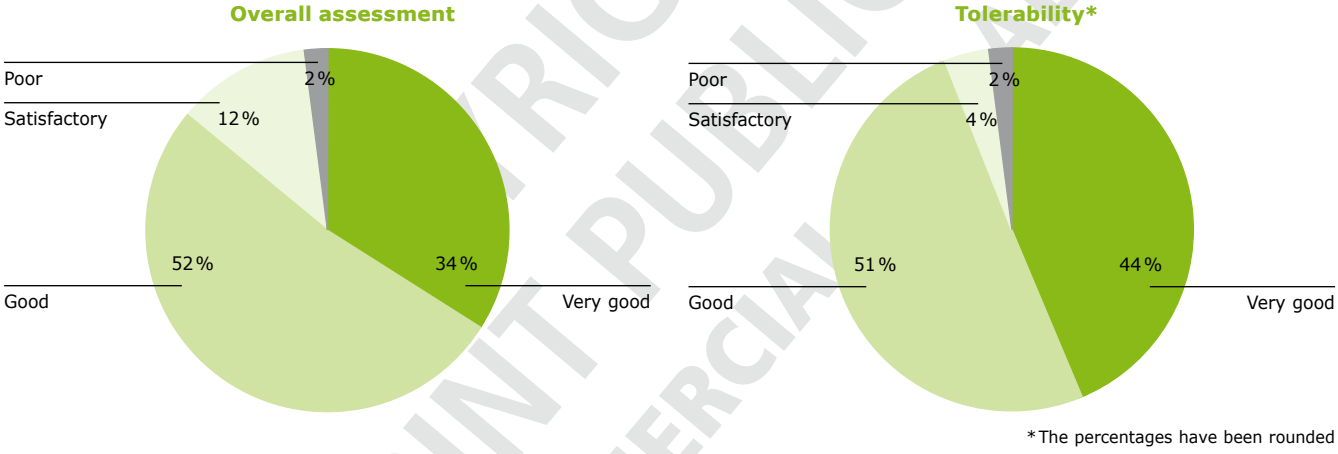

Figure 3. Overall assessment and tolerability of treatment with the 6-month depot LHRHa as rated by the treating physicians

In the present study, the physicians rated the treatment as very well or well tolerated in 95 % of the patients, which is in accordance with the results previously described by Tunn et al..[4]

Despite the limitations of observational studies, the descriptive analysis of the results of the present study clearly demonstrated the good efficacy and tolerability of the 6-month depot formulation of leuprorelin acetate in microcapsule form, which is comparable to the findings reported by Tunn et al..[4] As part of an individualized patient approach, physicians can thus choose between 1, 3, or 6-month depot formulations, depending on the desired visit interval.

5. Conclusion

The 6-month depot formulation of leuprorelin acetate in microcapsules (Sixantone®) opens a new dimension of flexibility for urologists and patients in planning treatment with LHRH agonists, thus allowing a more individualized and patient-oriented treatment. In the uro-oncological setting, 3 and 6-month depot formulations are ideal for the routine care of patients with advanced, hormone-responsive prostate cancer, who usually see their urologist every 3 or 6 months.

A 6-month depot formulation reduces the required number of injections, and hence, the incidence of injection-related

adverse effects; it also diminishes the psychological and physical stress associated with this invasive treatment, and avoids frequent confrontation with their illness in these typically elderly patients. Thus, 6-monthly injections may improve both quality of life and treatment acceptance.

Conflict of interest

All authors state that they have no conflicts of interest.

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Key Practice Issues

- Experience for over 20 years with the use of depot formulations of leuprorelin acetate in microcapsules has shown that it is a highly effective treatment for prostate cancer.
- The 6-month depot formulation has also demonstrated reliable efficacy in all patient subgroups and was well tolerated, thus expanding the available spectrum of effective depot treatments.
- The decision for a 1, 3 or 6-month depot formulation can be made on a case-by-case basis, depending on how often a patient wants or must visit their treating physician.

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