ORIGINAL RESEARCH

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Comparing the Efficacy of GnRH Agonists on the Castration Levels of Metastatic Prostate Cancer; Leuprolide Acetate 22.5 mg vs. Goserelin Acetate 10.8 mg

Metastatik Prostat Kanseri Tedavisinde Kullanılan Leuprolide Asetat 22,5 mg ile Goseraline Asetat 10,8 mg İlaçlarının Karşılaştırılması

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Abstract

Objective: We aimed to evaluate the effects of leuprolide 22.5 mg and goserelin 10.8 mg on castration levels in patients with metastatic prostate cancer.

Method: We evaluated 50 metastatic prostate cancer patients between 01.06.2012-01.06.2014, retrospectively. Of the patients, 25 received leuprolide 22.5 mg and 25 received goserelin 10.8 mg. Patients were followed up for 2 years and testosterone, prostate specific antigen (PSA) values were checked in every 3-months periods.

Results: The mean age of the patients were 64.48±8.18 and 65.52±7.93 years in leuprolide 22.5 mg and goserelin 10.8 mg groups, respectively (p=0.466). The mean Gleason score of the patients in both groups were similar (7.80±0.95 vs 7.84±1.17, p=0.949). Two (8%) patients treated with leuprolide and three (12%) patients treated with goserelin had testosterone levels above castration during follow-up. There were no statistically significant differences between the two groups in terms of reaching castration levels (p=0.641). There were no statistically significant differences between the drugs in the duration of exceeding from the castration levels (16.5 months vs. 13 months, p=0.4). In both groups, patients with low Gleason score (<9), single organ metastasis at the time of diagnosis, and PSA values of 2.5 ng/mL and below remained castrated for a longer period of time.

Öz

Amaç: Çalısmamızda metastatik prostat kanseri tedavisinde kullanılan leuprolide acetate 22,5 mg ile goseraline acetate 10,8 mg ilaçlarının kastrasyona etkilerini karşılaştırmayı amaçladık.

Yöntem: Kliniğimizde 01.06.2012 ile 01.06.2014 tarihleri arasında metastatik prostat kanseri tanısıyla löprolide 22,5 mg ve goserelin 10,8 mg tedavisi almış hastalar retrospektif olarak değerlendirildi. Her grupta 25 kişi yer aldı. Birinci gruptaki hastalara löprolid 22,5 mg, ikinci gruptaki hastalara goserelin 10,8 mg tedavisi başlandı. Hastalar 2 yıl süre ile takip edildi. Testosteron, prostat spesifik antijen (PSA) değerleri üç aylık sürelerle kontrol edilerek kastrasyona olan etkileri karşılaştırıldı.

Bulgular: Her iki gruptaki hastaların ortalama yaşları 64,48±8,18 ve 65,52±7,93 (p=0,466) idi. Löprolid ile tedavi edilen hastaların ortalama Gleason skoru 7,80±0,95 goserelin ile tedavi edilen hastaların ortalama Gleason skoru 7,84±1,17 olarak saptandı (p=0,949). Löprolid ile tedavi edilen iki hastada (%8), Goserelin ile tedavi edilen üç (%12) hastada takipleri sırasında testosteron seviyeleri kastrasyon seviyesinin üzerinde bulundu. İki grup arasında istatistiksel olarak anlamlı fark yoktu (p=0,641).

Sonuç: Her iki grupta da kastre düzeyin üzerine çıkan hastalar karşılaştırıldığında anlamlı bir fark saptanmadı. Ancak tanı anında Gleason skoru daha düşük olan (<9), tek organ metastazı saptanmış, PSA değerleri daha düşük (<2,5 ng/mL) olan hastalar kullandıkları ilaçtan bağımsız olarak daha uzun süre kastre seviyede kalmıştır.

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Abstract

Conclusion: Both leuprolide 22.5 mg and goserelin 10.8 mg are effective in achieving castration levels among metastatic prostate cancer patients. However, patients with low Gleason score (<9), single organ metastasis at the time of diagnosis and PSA values of 2.5 ng/mL and below remained castrated for a longer period of time.

Keywords: Castration, GnRH agonist, goserelin, leuprolide, LHRH agonist, prostate cancer, testosterone

Öz

Anahtar kelimeler: Goserelin, GnRH agonisti, kastrasyon, leuprolide, LHRH agonisti, prostat kanseri, testosteron

Introduction

Prostate cancer is the most common cancer in men (1). It is the second leading cause of death from malignant tumors after lung cancer (1). The majority (75%) of newly diagnosed cases are localized prostate cancer, and their overall survival rates are very high (2). On the other hand, the overall survival rate of metastatic prostate cancer ranges from 25% to 30% at 5 years (2). Prostate cancer cells are highly sensitive to the manipulation of the androgens and castration is causing prostate cancer cell death (3). In 80-85% of men with metastatic prostate cancer, androgen suppression can provide an average of 12-33 months of progression-free survival (4). Medical and surgical methods are used to suppress androgens in advanced prostate cancer (4). Bilateral orchiectomy can be performed for surgical castration (5). Luteinizing hormone-releasing hormone (LHRH) analogs, LHRH antagonists, steroids and non-steroidal antiandrogens can be used to achieve medical castration (4). LHRH analogs can be used in depot form for 1, 3 and 6 months (5) and it aims to keep testosterone levels below the level of castration (<50 ng/dL) (6). In our study, we aimed to compare the effects of leuprolide 22.5 mg and goserelin 10.8 mg, which are used as gonadotropin-releasing hormone (GnRH) agonists in metastatic prostate cancer for two years.

Materials and Methods

We evaluated 50 patients who were diagnosed with metastatic prostatic cancer in our clinic between 01.06.2012-01.06.2014, retrospectively. There were 25 metastatic prostatic cancer patients in each group. Leuprolide 22.5 mg was given to the patients in the first group, and goserelin 10.8 mg to the patients in the second group. Non-metastatic patients, those who had previously received hormone therapy, and orchiectomized patients were excluded from the study. Patients were followed up for 2 years and serum testosterone and prostate specific antigen (PSA) levels were evaluated once in every three months. Castrated serum testosterone level was defined as ≤50 ng/dL. Patients provided their written informed consent and the study was approved by the institutional review board (June 09, 2014-subject 197).

Statistical Analysis

Chi-square and Student's t-test were used as needed. Analyses were performed using the SPSS 10.0 statistical program. $p<0.05$ was accepted as statistically significant.

Results

The mean age of the patients was similar in leuprolide and goseroline groups (64.48±8.18 and 65.52±7.93, p=0.466). The mean Gleason score of the patients in the leuprolide and goseroline groups were (7.80±0.95 vs. 7.84±1.17, respectively (p=0.949). The castration level was exceeded in 2 (8%) and 3 (12%) patients in leuprolide and goseroline groups respectively and the rates were similar in groups (p=0.641). Twelve patients (48%) in the leuprolide group and 9 patients (36%) in the goserelin group and had single organ metastases whereas 13 (52%) patients in the leuprolide group and 16 (64%) patients in the goserelin group and had multiple organ metastases (p=0.395) (Table 1). Mean testosterone levels were 0.28 ng/mL at the third month in the goserelin treatment group, and 0.26 ng/mL in the leuprolide treatment group (p=0.592). The castration level was exceeded in an average of 13 months in patients receiving goserelin treatment, and in an average of 16.5 months in patients receiving leuprolide treatment. There were no statistically significant differences between the two groups (p=0.4). The mean PSA values at the third month were 5.2 ng/mL in the goserelin group, and 3.87 ng/mL in the leuprolide group (p=0.376).

At the end of the 2-year follow-up, 5 (10%) patients in both groups had testosterone levels above the castration level. The mean Gleason score of these patients was 9.0±1.0 and that of 45 patients who remained at the castrated level was 7.68±0.99 (p=0.078). The mean PSA values in the

2-year follow-up were significantly higher among patients whose testosterone levels were above the castration level (5.26±4.89 vs. 2.36±8.31, p=0.021), (Table 2). The percentage of prostate cancer patients who had multiple organ metastases at the time of diagnosis was higher among patients whose testosterone levels were above the castration level (80% vs. 55.5%, p=0.298).

Discussion

In our study, testosterone levels were found higher than castration level in a total of 3 patients (median at 13 months) in the goserelin 10.8 mg treatment group, and in 2 patients in the group using leuprolide 22.5 mg treatment (median at 16.5 months). There were no significant differences between the two groups in terms of the time period of exceeding castration levels. We have observed that testosterone levels rise above the castration level earlier in patients with higher PSA value, multiple organ metastases and a Gleason score of 9 and above, regardless of the GnRH agonist used.

Even if the PSA levels are very low, there is a risk of prostate cancer (7% can be detected when PSA is <0.5 ng/mL). Gleason scoring is used when evaluating pathological preparations and is an important prognostic indicator. A Gleason score of 8-10 was used for poorly differentiated, 5-7 for moderately differentiated and 2-4 for well-differentiated cancer (7). Despite early diagnosis and progress in treatment, approximately 25% of patients progressed to metastatic disease.

A high Gleason scores is associated with more aggressive metastatic prostate cancer progresses (8). In a study of 28 patients, Nishiyama et al. (8) showed that the level of testosterone remained as castrate for a longer time in patients with a Gleason score <7 who received GnRH agonist therapy (9). In our study, a total of five (10%) patients in the entire study group had testosterone above the castration level. The mean Gleason score of these patients was 9.0±1.0 and that of the 45 patients who remained at the castrated level was 7.68±0.99. Low Gleason score at the time of diagnosis was associated with longer castration period (p=0.078).

Similarly, Fujii et al. (9) compared the effects of GnRH agonists on castration levels in the treatment of metastatic prostate cancer. In their study in which a total of 232 patients participated, 1- and 3-months forms of leuprolide and goserelin were compared. Forty patients received monthly leuprolide acetate, 68 patients received 3-months leuprolide acetate, 50 patients received monthly goserelin acetate, and 74 patients received 3-months goserelin acetate treatment. The mean testosterone levels after 3 months were 0.23 ng/mL, 0.21 ng/mL, 0.18 ng/mL, 0.21 ng/mL. Testosterone levels exceeded castrated levels (0.55-0.65 ng/mL) in 1 patient using the 1-month form of leuprolide acetate and 1 patient using the 3-month form

Table 1. Socio-demographic and clinical data of the patients

	Goserelin acetate 10.8 mg	Leuprolide acetate 22.5 mg	p-value
Age	65.52±7.93	64.48±8.18	0.466
Gleason score	7.84±1.17	7.8±0.95	0.949
Above castration level	3 (12%)	2 (8%)	0.641
Single organ metastasis	9 patients (36%)	12 patients (48%)	
Multiple organ metastasis	16 patients (64%)	13 patients (52%)	0.395
Average testosterone levels after 3 months	0.28 ng/mL	0.26 ng/mL	0.592
Average time above castration level	13 months	16.5 months	0.4
Mean PSA levels at diagnosis	92.35 ng/mL	77 ng/mL	
Average PSA levels after 3 months	5.2 ng/mL	3.87 ng/mL	0.376

PSA: Prostatic specific antigen, Student's t-tests, p<0.05 as statistical significance level

Table 2. Clinical values of the castrate and castration resistant patients

	Patients above castration level	Castrated patients	p-value
Single organ metastasis	1	20	
Multiple organ metastasis	4	25	0.298
Gleason score	9±1	7.68±0.99	0.078
Average PSA value	5.26±4.89	2.36±8.31	0.021

PSA: Prostatic specific antigen, chi-square test, p<0.05 as statistical significance level

of goserelin acetate. There was no statistically significant difference in reaching to the castration levels (10). In our study, median testosterone levels were 0.28 ng/mL at the 3rd month in patients using the 3-month storage form of goserelin acetate and 0.26 ng/mL in patients using the 3-month storage form of leuprolide acetate (p=0.592). All patients remained at castrated levels at the 3rd month of the treatment.

In another study by Dias Silva et al. (10) the u medical castration duration of leuprolide 3.75 mg, 7.5 mg and goserelin 3.6 mg drugs were compared. Three groups, each consisting of 20 patients were formed. After 3 months of treatment, 26.3% of patients using leuprolide 3.75 mg, 25% of patients using leuprolide 7.5 mg, and 35% of patients using goserelin 3.6 mg did not reach castrated levels (cut-off <50 ng/mL). When the cut-off was taken as <20 ng/mL, 68.4%, 30% and 45% of the patients could not reach to castrate levels. No significant differences were found between the groups in terms of reaching to the castration levels (11). In our study, a total of 25 patients using goserelin 10.8 mg and 25 patients using leuprolide 22.5 mg participated in the study. All of the patients reached castrate levels at the 3rd month of the treatment; however, 3 patients and 2 patients in the goserelin 10.8 mg and leuprolide 22.5 mg groups had testosterone levels above castrated levels at an average of 13 months and 16.5 months, respectively (p=0.4).

Fontana et al. (11) evaluated the efficacy and side effects of goserelin 10.8 mg. A total of 115 patients diagnosed with locally advanced prostate cancer or metastatic prostate cancer participated in the study. Testosterone levels decreased to castrated levels by the end of four weeks in all patients. PSA reduction occurred in 86% (99/115) of the patients and none of the patients developed an injection site reaction. Goserelin acetate 10.8 mg was reported to be safe and effective (11). In our study, testosterone levels decreased to castrated levels in all patients in the 3rd months, and a significant decrease was observed in the PSA values (p=0.036). No reaction was observed at the injection site in any of the patients.

Study Limitations

The main limitation of this study was the small number of patients recruited from a single center. Future multi-center studies with more metastatic prostate cancer are required to confirm our study findings.

Conclusion

There were no statistically significant differences in achieving castration levels and the duration to reach castration levels between leuprolide 22.5 mg and goserelin 10.8 mg. Testosterone levels increased earlier among patients with a Gleason score ≥9, multiple organ metastases and higher PSA values. Larger studies are needed to better evaluate the efficacy of these drugs.

Ethics

Ethics Committee Approval: Gaziantep University Clinical Research Ethics Committee (May 20, 2012-subject 124) gave permission to conduct the study.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: G.Ç., F.Y., Design: G.Ç., F.Y., Data Collection or Processing: G.Ç., Analysis or Interpretation: G.Ç., F.Y., Critical Revision of Manuscript: G.Ç., F.Y., Drafting Manuscript: G.Ç., Final Approval and Accountability: G.Ç., F.Y., Writing: G.Ç., F.Y.

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