



The Adherence to Hormonal Deprivation Therapy for Prostate Cancer in a Real Life Contest: Retrospective, Single-Centre Study

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Abstract

Introduction and Objectives: The Androgen Deprivation Therapy (ADT) is one of the therapeutic options for the treatment of prostate cancer (PCA), both for the advanced forms and metastatic forms, in a neoadjuvant or adjuvant setting, alone or in combination with surgery or radiotherapy (RT). Aim of the study is to appraise the adherence to the ADT.

Material and Methods: Patients with diagnosis of PCA, for which an ADT (leuprorelin, triptorelin or degarelix) has been prescribed, have been followed between January 2008 to December 2015. Demographic, histopathological and clinical data were collected.

Results: 136 patients (mean age 76y and PSA 91.9 ng/ml) were followed over time. At diagnosis, 34% had a Gleason Score >7; 108 patients were exclusively treated by ADT: the drugs were prescribed as follow: 49% leuprorelin, 42% triptorelin, 9% degarelix. The mean follow-up was 3.5y, with a mean years of prescription of 3.4. Therefore the adherence was 98%. Of the 108 patients available for the analysis, 63 are currently treated by ADT, while 45 have stopped. The causes for discontinuation were: death, physician's choice and patient's preference in 56%, 33% and 11% of the cases, respectively.

Conclusions: Today we have little and rarely data the data on patient's adherence to ADT in the literature. On the basis of our results we highlight an adherence to the ADT close to 100%: it's a regimen with high adherence.

Keywords: Prostate cancer; Androgen deprivation therapy; Adherence

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Introduction

Prostate Cancer (PCa) represent the second most common cancer in men and the sixth cause of cancer-related death (6%) in worldwide [1]. Androgen-Deprivation Therapy (ADT) is the standard first-line therapy for metastatic PCa [2,3]; is also frequently used to treat men with non metastatic PCa [4]. Huggies and Hodges had introduce androgen suppressing strategies in the management of advanced PCa like a unimodal or multimodal approach. ADT improves progression free survival and overall in men with advanced PCa like adiuvant approach after radiotherapy [5,6] or after radical prostatectomy with histologically positive margins or lymph nodes [7]. ADT is also commonly used in patients with increasing prostate cancer specific antigen (PSA) level after primary treatment. The cancer treatment adherence is crucial to obtain optimal health outcomes and improvement in quality of life. The World Health Organization (WHO) firstly defined the meaning of patient's adherence pharmacological therapy as the extent to which a person's behaviour in taking medication corresponds to recommendations given by a health care provider and which that individual has agreed upon [8,9]. This definition was been completed later by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as "the extent to which a patient participates in a treatment regimen after he or she agrees to that regimen" [10,11]. The non adherence to pharmacological therapy showed a decreased survival [12,13], higher recurrence/treatment failure rates [14,15] and health care costs [12,16-18]. The Adherence is a multidimensional phenomenon, and according to the WHO, is influenced by patient-related, therapy-related, condition-related, health system and social economic factors [17]. The causes of non adherence in oral chemotherapy and /or hormonal therapy in the older population are caused by the increasing number of prescribed medications [19,20] and it has been described to reach 50% [21,22]. The adherence to the ADT in men with PCa is unknown. The aim of this study is to evaluate the adherence about ADT in patients

Table 1: Sociodemographic and clinical characteristics of the patients.

Variable	
Number of patients (n)	136
Median age (range)	76 (53 – 87)
Marital status, n	
-married	76
-unmarried/divorced	41
-widower	19
Work Status, n	
- retired	82
- artisan	22
- missing	32
Region of Residence, n (%)	
- Abruzzo	90 (66)
- Molise	43 (32)
- Campania	3 (2)
Year of diagnosis prostate cancer, n (%)	
-2008	9 (7)
-2009	20 (15)
-2010	15 (11)
-2011	24 (17)
-2012	19 (14)
-2013	17 (12)
-2014	12 (9)
-2015	20 (15)
EDR, n (%)	
-Negative	35 (26)
-Positive	45 (33)
-Missing	56 (41)
Median PSA (range), ng/ml	91.9 (3.3 – 2900)
Biopsy Gleason score, n (%)	
-≤7	90 (66)
->7	46 (34)
Therapeutic approaches, n (%)	
-Radical Prostatectomy	10 (7.5)
-External beam radiation	29 (21.5)
-Prostatectomy + External beam radiation	3 (2)
-ADT alone	62 (45)
-Missing	32 (24)
Indication of ADT, n (%)	
-Physician decision	57 (42)
-Adjuvant RP	3 (2)
-Adjuvant RT	18 (13.5)
-Neoadjuvant RP	4 (3)
-Neoadjuvant RT	10 (7.5)
-Biochemical recurrence	8 (6)
-Patient decision	1 (1)
-Metastases	3 (2)
-Missing	32 (23)

with PCa in a “real life” setting.

Materials and Methods

We retrospectively analyzed patients with histologically diagnosed PCa in the Department of Urology, “S. Pio da Pietrelcina” Hospital, in Vasto (Italy) from 1st January 2008 to 31st December 2015, treated with ADT in a neoadjuvant or adjuvant setting, as single agent therapy or as a part of multimodal approach. The prescribed drugs were leuprorelin, triptorelin or degarelix. Only LHRH agonists and antagonists were considered in the analyses (ATC codes, respectively L02AE and L02BX02). The first prescription of a ADT was considered the index date for patient inclusion. The index period was the time between the index date and the last prescription of ADT. ADT adherence was measured only in patients that receiving ADT for a minimum of 3 months during the index period. The ADT prescriptions were periodically checked with a paper form compilation according to the Italian rules of appropriate drug regimen. This form called “Annual Therapeutic Plan” (ATP) and it's done by urological or oncological centres. ATP has a periodical deadline: all the patients were periodically visited to evaluate the benefits of ADT therapy and

Table 2: Treatment details.

Variable	
Drug prescribed n (%)	
-Leuprorelin	53 (49)
-Triptorelin	45 (42)
-Degarelix	10 (9)
Mean Follow-up, years	3.5
Mean Overall prescription, years	3.4
Adherence Rate, %	98
Patients discontinued, n (%)	
-Currently treating	63 (59)
-Discontinuation therapy	45 (41)
Causes for discontinuation therapy, n (%)	
- Death	25 (56)
- Physicians' choice	15 (33)
- Patients' preference	5 (11)

to re-filled ATP. The reasons for discontinuous ADT were recorded for each case and classified in: patient's choice, physician's choice, patient's death. We excluded patients without complete information.

Statistical Analysis

Means, medians, and inter quartile ranges were used for continuous variables: frequencies and proportions were reported for categorical variables. The t-test, the Mann-Whitney test, and chi-square tests were used to compare the different statistical significance in means, medians, and proportions, respectively.

All statistical tests were performed using R software environment for statistical computing and graphics (Vienna, Austria, version 3.0.1). All tests were two-sided, with a significance level set at $p < 0.05$.

Results

We enrolled 136 patients: sociodemographic, pathological and clinical parameters were analyzed and are detailed in Table 1. Treatment details are reported in Table 2.

The median age was 76 (range 53.0-87.0) years and the median PSA was 91.9 (range 3.30 – 2900.0) ng/ml. At the time of the diagnosis, 45 patients (33%) had digital rectal examination (EDR) positive and 46 (34%) had a Gleason score >7 at the prostate biopsy. The patients were primarily treated with Radical Prostatectomy (RP), Radiotherapy (RT), RP + adjuvant RT and with primary ADT in 10 (7.5%), 29 (21.5%), 3 (2%), 62 (45%), respectively. As neoadjuvant strategy, the ADT was used in 7.5% of cases in conjunction with RT. In an adjuvant setting the ADT was used in 13.5% and 2% of cases in conjunction with RT and RP. The ADT was used in 108 patients, we missing 24% (n = 28) of the patients because the date were incomplete and we didn't include in this study. We prescribed leuprorelin, triptorelin and degarelix in 53 (49%), 45 (42%), 10 (9%) patients, respectively. The median follow-up was 3.5 years, with a mean overall prescription of 3.4 years. The adherence about ADT was respected in 98% of patients: 63 patients are currently treated with ADT, while 45 have stopped. The causes for discontinuation therapy were death, physician's choice and patient's preference in 56%, 33% and 11% of the cases, respectively.

Discussion

In the treatment of PCa, the use of GnRH analogues, such as Leuprorelin, Triptorelin and Degarelix, it must be continued for a long time. The discontinuous therapy represent a cause of loss of the adherence, could be represent a cause of non-response to the therapy and a consequent increase of the cost for the economic

healthy resource. As concerning the poor adherence to adjuvant endocrine treatment for breast cancer is a well known problem [23]. On the other hand, there are few studies evaluating the adherence to therapy with GnRH for men with PCa. Most of the studies are focused on adherence to oral therapy in patients with breast cancer or androgen blockade in patients with PCa. Used a randomized phase III trial to evaluate adherence to long-term androgen blockade (1 month treatment of 50 mg bicalutamide daily plus 18 or 36 months of luteinizing hormone-releasing analogs) in patients with localized high-risk prostate cancer in Canada [22]. They found that 93% of patients adhered strictly to 1 month of bicalutamide treatment. Others studies, about adherence, reported that factors such as having age ≥ 75 years [24], being unmarried, having several comorbidities or having lymph node-negative disease were associated with higher adherence and persistence to therapy [25], while others reported the same factors being associated with greater non-adherence and non-persistence [26]. The results of our survey show that for the treatment of PCa Leuprorelin, Triptorelin and Degarelix, the patients were adherent to treatment in the study period (between 2008 to 2015). The treatment was interrupted almost exclusively for the patients' death or physician's choice. The medication adherence data were very good considering the old age of the patients: it shows that the age factor does not affect the therapy. Also the length of the treatment does not decrease the medication adherence [25]. This evidence is supported by the constant check-up of the patient by the specialist that renew the treatment once per year, infact in Italy this drugs can be annually prescribed only by a specialist in urology or oncology, with the redaction of a specific therapeutic plan, and, on this basis, the family doctor can prescribe.

Conclusion

This retrospective study found that during the 8-years observation period, the most patients treated for prostate cancer perform the therapy with GnRH therapy since the adherence to the ADT is close to 100%.

In conclusion the ADT is a long term therapy with high adherence rate.

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