ORIGINAL RESEARCH

THE COMPARISON OF THE EFFICACY OF CYPROTERONE ACETATE AND CASTRATION MONOTHERAPIES IN METASTATIC PROSTATE CANCER: A MULTICENTER STUDY OF A TURKISH URO-ONCOLOGY GROUP

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ABSTRACT

Objective: To detect the therapeutic efficacy of CPA and to compare it with surgical or medical castration in advanced prostate cancer

Patients and Methods: Patients from 19 Urology Centers with prostate adenocarcinoma of stages T1-4N+MX or T1-4NXM+ were enrolled. A total of 120 patients were randomized to receive CPA 3X100mg/d(Group 1) versus medical or surgical castration(Group 2).The primary endpoints for this trial were overall and disease-spesific survival.Progression-free survival(PSA progression time) and testosterone decrease rate were assessed as secondary endpoints.Progression-free survival probabilities were calculated by the Kaplan-Meier method and comparison of survival probabilities was performed by the Logrank test.

Results: The median PSA values were 42ng/dl in both groups at initiation and decreased to 3.0 and 2.1 respectively in 3 months($p>0.05$).Castrate testosterone levels were reached in two groups after 3 months therapy(9% and 6.7% of initial values respectively;$p>0.05$).The data is immature to assess the survival durations,but in median follow-up of 24 months,no difference in regard to PSA-progression was detected in the two groups($p=0.616$).

Conclusion: This randomized study of CPA and castration in patients with metastatic prostate cancer has not so far revealed any significant differences in progression-free survival.The initial efficacy and tolerability of monotherapy encourages us to comment that this therapy is safe and acceptable.

Keywords: Prostate cancer,Cyproterone acetate,Castration,PSA-progression,Survival

METASTATİK PROSTAT KANSERİNDE CYPROTERONE ACETATE VE KASTRASYON MONOTERAPİLERİNİN ETKİNLİĞİNİN KARŞILAŞTIRMASI: ÇOK MERKEZLİ BİR TÜRK ÜRO-ONKOLOJİ GRUBU ÇALIŞMASI

ÖZET

Amaç: İlerlemiş prostat kanserinde tibbi veya cerrahi kastrasyon ile CPA'yi karşılatırmak ve CPA'nin terapötik etkisini ortaya koymak.

Gereç ve Yöntem: Ondokuz Üroloji Merkezi'ne başvuran T1-4N+MX veya T1-4NXM+ evreli prostat adenokanserli hastalar çalışmaya alınmıştır. Toplam 120 hasta, CPA 3X100mg/gün (Grup1) ve tıbbi veya cerrahi kastarasyon (Grup 2) gruplarına rastgele dağıtılmışlardır. Bu denemenin birincil son noktaları genel ve hastalığa-özel sağkalım olasılıklarıdır. Progresyonsuz sağkalım (PSA progresyon zamanı) ve testesteron düşüş hızı ikincil son noktalar olarak kabul edilmiştir.Progresyonsuz sağkalım olasılıkları Kaplan-Meier metoduyla hesaplanmış ve Logrank testiyle de sağkalım olasılıkları karşılaştırılmıştır.

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Bulgular: Başlangıçta her iki grupta da PSA ortanca(medyan) değerleri 42ng/dl bulunmuş ve 3 ayda Grup1'de 3.0 'e Grup2'de de 2.1'e düşmüştür (p>0.05). Her iki grupta da 3 aylık bir tedavi sonrasındaki testesteron seviyeleri başlangıçtaki değerlerin Grup1'de % 9'una Grup2'de %6.7'sine ulaşmıştır (p>0.05).Her ne kadar veriler sağkalım süreleri için tam olmasa bile, ortanca 24 aylık izlem süresinde PSA-progresyonu için iki grup sağkalımlarında bir fark bulunmamıştır (p=0.616).
Sonuç: Yaptığımız bu randomize çalışma, CPA ve kastrasyon tedavisi alan prostat kanserli hastalarda progresyonsuz sağkalım bakımından 24 aylık izlem zarfında herhangi bir anlamlı faklılık ortaya koymamıştır. Monoterapinin başlangıçtaki etkinliği ve tolerabl olması bu terapinin kabul edilebilir ve güvenilir bir tedavi olduğu yorumlarında bizi cesaretlendirmektedir.
Anahtar Kelimeler: Prostat kanseri,CPA,Kastrasyon,PSA-progresyon,Sağkalım

INTRODUCTION

Prostate cancer is an androgene hormone-responsive tumour and is generally controlled by removal of the androgenic stimulus [1,2]. Surgical castration has been considered the "gold standard" treatment for metastatic prostate cancer [3] and most studies concerning other hormonal therapies for metastatic disease have used bilateral orchidectomy as the comparator.On the other hand,studies demonstrate that luteinizing hormone releasing hormone (LHRH) agonists such as goserelin are as effective as orchidectomy [4,5].

In the 1980's, maximum androgene blockade (MAB) gained a wide acceptance among urologists for the treatment of metastatic prostate cancer.However,after the report of a meta-analysis of 27 of these studies which indicated only a small difference in overall survival at 5 years in favor of MAB [6,] enthusiasm subsided. As there is clear evidence of the limited clinical value of MAB in the treatment of metastatic prostate cancer today; attention is again focused on monotherapy. If this is as effective as MAB, quality of life and cost-effectiveness would indicate monotherapy.Another recent issue is the use of oral antiandrogens such as monotherapy in the treatment of metastatic prostate cancer.Until recently, antiandrogens were only used as a component of MAB, but increasing evidence suggests that monotherapy with certain antiandrogens is an attractive alternative to castration-based therapy.The first antiandrogen in widespread use was the steroidal compound cyproterone acetate (CPA) followed by the nonsteroidal antiandrogens bicalutamide, flutamide and nilutamide [7,8,9].

This trial aimed to detect the therapeutic efficacy of CPA and compare it with surgical or medical castration in a group of patients with locally advanced and/or metastatic prostate cancer with a relatively favorable prognosis.The primary end-point of this study was the mean overall and disease-spesific survival times in the treatment groups. Secondary end-points were the comparison of the treatment arms with respect toprostate specific antigen (PSA)-progression and castrate testosterone levels.

PATIENTS AND METHODS

This was a multicenter, prospective, randomised study conducted at 19 Urology Centers in Turkey. The aim of the trial was to compare the efficacy of CPA with surgical or medical castration in metastatic prostate adenocarcinoma.

Eligibility Criteria and Allocated Treatments

Patients with WHO performance status of 0-2 were eligible if they had measurable lymph node or soft tissue metastasis.Patients with detectable bone metastasis were also included (T1-4 N+MX or T1-4 NXM+). Since we aimed to include patients with a relatively favorable prognosis,patients with PSA values ≥100 ng/dl were not enrolled in the study. The other exclusion criteria were; histopathologic diagnosis other than adenocarcinoma, presence of cardiovascular and gastrointestinal problems which required medical therapy and liver enzyme elevations more over twice the normal levels. Furthermore, patients who had received previous hormonal therapy and radiotherapy to the metastatic sites were also excluded.

The study was conducted in accordance with respective European regulatory requirements, including the 1975 Declaration of Helsinki. Written consent was obtained from the ethics commitees of each participating center. A total of 120 patients were randomised to receive CPA (3x100mg/day orally) (Group 1, N: 60) versus medical or surgical castration (Group 2, N: 60). Patients randomised to the second treatment arm recommended surgical castration as the treatment procedure.In patients who refused surgical castration, medical castration by LHRH analogs was initiated. Any available LHRH agonists were acceptable in this respect.

Baseline examinations included complete blood counts and biochemical tests (including PSA and testosterone measurements), computed tomography (CT) scan of the abdomen and pelvis and bone scintigraphy. Clinical examinations and biochemical tests were repeated every 3 months and bone scans were repeated every 12 months or as required.After disease progression or patient withdrawal from the therapy for any reason,patients were followed until death.On progression, treatment changes were left to the discretion of the investigator.

Endpoints and Evaluation of Efficacy

The primary endpoints for this trial were overall and disease-spesific survival. Progression-free survival (PSA –progression) and testosterone decrease rate after the initiation of therapy were assessed as secondary endpoints. Progression was defined as the appearance of new metastatic sites (objective) or increase in PSA, increase in pain by two scores and worsening of the performance status by two scores (subjective). Since this interim analysis was focused mainly on PSA-recurrence, PSA monitoring received the major attention; and increase in PSA value by 20% or more on two consecutive determinations one month apart was considered as biochemical recurrence.Progression-free survival was computed from the date of randomization to the date of disease progression.All of the events and side effects were reported to the Data Center as encountered.

Quality control of the data and study performance were carried out in several steps. This included data verification and randomization by the data manager in the Data Center, review of patients' documents for eligibility, compliance and endpoints by the Study Coordinator, and finally, computerized verification for errors and inconsistencies was carried out by the statistician.

Size of Trial Population and Statistical Analysis

Sample size:

We initially estimated 381 patients to be recruited in the study with the power =0.80 and α=0.05. Median survival time to progression was considered 18 months for the CPA group and 23 months for the castration group.

Accrual time during which patients were recruited and additional follow-up time after the end of recruitment were considered as 36 months and 18 months respectively.

The trial accrued less than one third of the number of patients required because of some inconveniences in recruitment, mostly due to the restrictions of the inclusion criteria.

Statistical Analysis:

Progression-free survival probabilities were calculated by the Kaplan-Meier Method.A comparison of Kaplan-Meier survival probabilities was performed by using the Logrank test. Comparisons of frequency distribution were performed by means of the X^2-test and of continuous random variables by means of the Wilcoxon rank sum (Mann-Whitney) test.

A p-value of less then 0.05 was considered significant. All p-values were two-sided.

RESULTS

The baseline characteristics and prognostic factors of the 120 randomized patients at entry were well-balanced between the two arms with respect to age,PSA value,node and metastatic status etc.The only parameters for which a significant difference in baseline values were noted as Alkalen phosphatase, Hb

and Htc.The patients baseline characteristics are shown in Table I.

As the study did not reach its maturity with respect to time; more emphasis was put on the PSA decline and PSA-progression.Median PSA values revealed a favorable decline in both groups and there was no statistical difference between the PSA values at 3,6 and 12 months in the two arms (Table II).

Another concern was whether median testosteron levels would reach the castration levels in both groups. Upon evaluation on the third month, the castrate levels of testosteron were achieved as 19.0 ng/dl (9% of initial value) and 17.0 ng/dl (6.7% of initial value) in Groups 1 and 2, respectively. This difference was also insignificant ($p>0.05$), (Fig.1).

The median follow-up period of the patients was 24 months (23 months in the CPA group and 24 months in the castration group). The number of events in the groups was 12 and 20 respectively (Table III). According to Log Rank test evaluations, there was no difference with regard to PSA-progression in the two groups in the 24 month follow-up($p=0.616$) (Fig.2).
There were a total of 10 deaths (4 in the first, 6 in the second group) so far. Only 4 (2 in both groups) were attributed to prostate cancer. Obviously in this step of the trial, survival data is not available; thus, the primary endpoints have not yet been reached. Further follow-up is awaited.

The overall safety profile of both treatments was acceptable. No severe cardiovascular and/or gastrointestinal side effects and/or increases in liver function tests or serum alkaline phosphatase changes have been encountered up to date ($p>0.05$) (Figs. 3a,b,c).

However, erectile dysfunction was universal and almost every patient has suffered from loss of libido and/or erectile disfunction.

Table 1. Patients' baseline characteristic

	CPA	**Castration**	**P Value**
Age (median,range)	75 (65-97)	75 (51-86)	0.235
Lymph node positivity*	15/38	14 / 45	0.426
Bone metastases	47/58	46 / 57	0.397
PSA values (median, range)	42(2.10-98) ng/dl	42 (5.6-99) ng/dl	0.825
Kreatinin (median,range)	1.04(0.10-6.32) ng/dl	1.1 (0.64-4.0) ng/dl	0.715
Alkalen phosphatase (median,range)	143(12-1565)	205 (39-1235)	0.011
Hb (median,range)	13.1(5.75-16.0)	13.7 (7.40-16.4)	0.009
Htc (median,range)	39.0(16.2-55)	40.6 (21.9-48.3)	0.01

*Not every patient was evaluated with CT

Table II. Median PSA decline after the treatment

	Baseline N, ng/dL (% initial value)	**3 months N, ng/dL (% initial value)**	**6 months N, ng/dL (% initial value)**	**12 months N, ng/dL (% initial value)**
CPA (Group1)	n=58, 42.0	n=51, 3 (7)	n=45, 1.35 (3.2)	n=22, 0.875 (2)
Castration (Group2)	n=57, 42.0	n=49, 2.13 (5)	n=46, 1.05 (2.5)	n=33, 0.87 (2)
p> 0.05 (in all comparisons)				

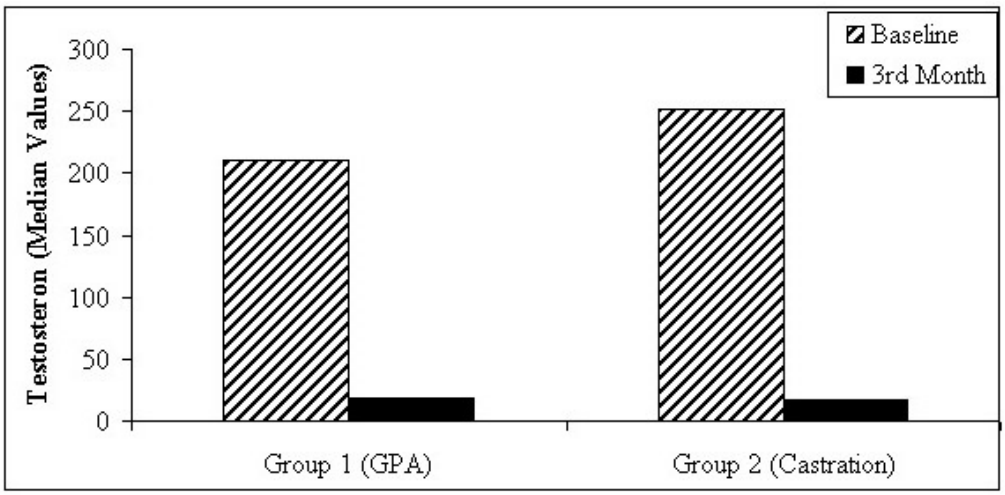

Fig. 1: Baseline and 3rd month testosterone median values in CPA (Group1) and Castration (Group 2) groups.

Table III. PSA-progression Analysis for Time

	Total	**No. events**	**No. censored**	**% censored**
Group 1 (CPA)	60	12	48	80.00
Group2 (Castration)	60	20	40	66.67
Total	120	32	88	73.33

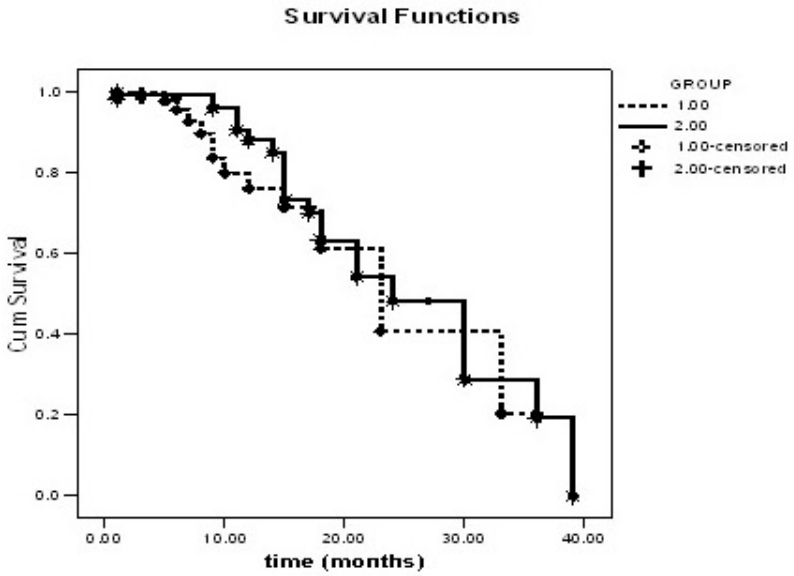

Figure 2: Progression-free Kaplan-Meier survival probabilities for CPA (group1) and Castration (group2) patients

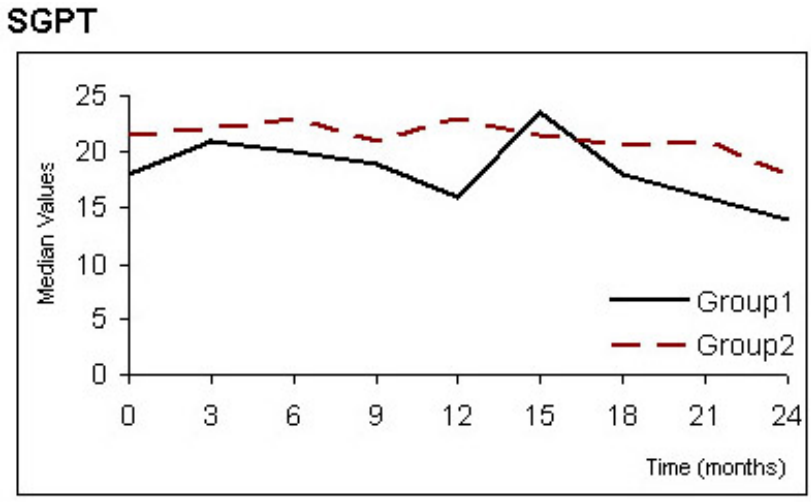

Figure 3a: SGPT median values in Group1(CPA) versus Group2 (Castration)

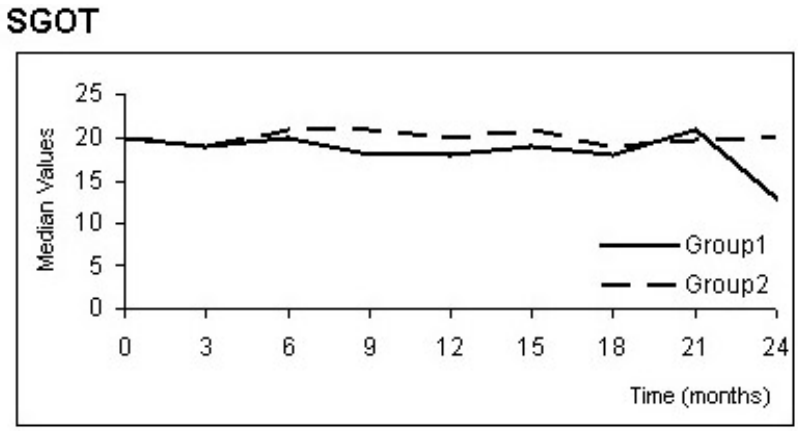

Figure 3b: SGOT median values in Group1(CPA) versus Group2 (Castration)

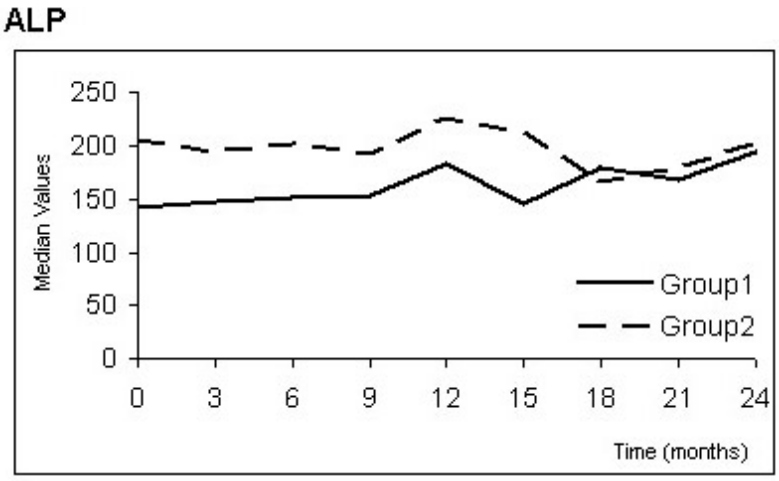

Figure 3c: Alkalene Phosphatase median values Group1 (CPA) versus Group2 (Castration)

DISCUSSION

Since the first observation by Huggins and Hodges in 1941 [2,] hormonal therapy remained the main therapeutic option for advanced prostate cancer. So far, multiple strategies have been used to reduce the serum levels of androgens or to interfere with their function via the androgen receptor (AR). The classical form of androgen deprivation is surgical castration by bilateral orchiectomy.This is the most immediate method to reduce circulating testosterone(T) by > 90% within 24 hours without any risk of a paradoxical flare of the disease [10]. Although surgical castration may be underused in our time,some studies suggest that many patients prefer this approach for reasons of convenience and cost[11]. Reversible medical castration dates back to the 1940's. This was achieved by the administration of dietylstilbesteol (DES), a semi-synthetic estrogen compound[12]. Due to the high incidence of cardio-vascular (CV) toxicity and gynecomastia observed in patients receiving DES; this sort of androgene ablation has generally been abondoned today[12,13]. The development of LHRH analogues, obtaining medical castration with significantly fewer CV events and lack of gynecomastia,has led to a dramatic change in the treatment of advanced prostate cancer. The side effects of LHRH agonists include hot flashes, loss of libido and osteoporosis[14,15].

Surgical or medical castration results in the disappearance or marginal decline of adrenal androgens that are likely to possess intrinsic androgenic activity[16]. Therefore, men who undergo castration still have relatively high levels (up to 40%) of DHT and 5-10% of T, presumably derived from adrenal precursors[17]. MAB as a concept of treatment for prostate cancer is the simultaneous complete elimination or blockade of testicular and adrenal androgens[18]. Since 1989, several randomized trials have suggested that MAB prolongs survival of the patients with advanced prostate cancer, compared to castration alone[19,20]. However, in 1998, Eisenberger et al.[21] reported a randomized trial of 1.387 patients with metastatic prostate cancer who were all treated with surgical castration with placebo or flutamide[21]. There was no statistically significant survival advantage in favour of MAB. In 2000, the Prostate Cancer Trialists' Collaborative Group performed a meta-analysis of 27 trials of MAB versus castration monotherapy involving 8.275 patients[6]. This study indicated a small difference in overall survival at 5 years in favor of MAB [25.4% vs 23.6%]. It is also reported that MAB is associated with more side effects,which have a negative impact on quality of life (QOL).

Since MAB has lost its initial popularity as an antiandrogen deprivation approach, a growing

interest has emerged in using antiandrogens as monotherapy in metastatic prostate cancer. The efficacy, tolerability and QOL benefits of bicalutamide (B) monotherapy vs castration were assessed in some phase III studies with locally advanced or metastatic prostate cancer[22-25]. Data emerging from these studies support the use of B monotherapy as an alternative to castration in patients with advanced disease, since the survival outcome is similar. However, this is true especially in well or moderately differentiated tumours;whereas, in patients with poor prognostic factors, antiandrogen monotherapy is inferior to castration in terms of overall survival and time to progression. CPA is a progestational antiandrogen and the first antiandrogen used for the treatment of advanced prostate cancer in Europe. It competes with androgens for the binding to the AR, as well as possessing antigonadotropic activity that results in a rapid and sustained 70-80% decrease in T levels[8,26]. There are limited and conflicting data on the use and effectiveness of steroidal antiandrogen CPA as a monotherapy in locally advanced and metastatic prostate cancer. In the first large phase III clinical study conducted by EORTC-GU Group[27], 295 locally advanced prostate cancer patients were randomised into three treatment groups as: DES 3 mg/day, CPA (250mg/day) and Medroxyprogesterone acetate (MPA) (500 mg 3 times a week im.). With respect to the response of the primary tumour there was no statistical difference between CPA and DES. When the "time to progression" was compared, there was no significant difference between CPA and estrogens. Overall survival, including all causes of death in these two groups, was also similar. MPA was not effective in preventing progression and survival times were shorter with this agent. A comperative study of CPA and castration has reported survival data[28]. This was an open randomized study which compared goserelin, DES and CPA in two different cohorts of patients (arms A and B). CPA was associated with significantly poorer median survival (64 weeks) than goserelin (>194 weeks) in arm A, but no difference was seen in arm B (130 vs 132 weeks, respectively). A further study comparing CPA monotherapy, goserelin and MAB (goserelin plus CPA) found that CPA was less effective than goserelin, but with similar results to the MAB regimen in terms of delaying progression. However, survival data was not available[29]. Therefore, it is difficult to draw any definite conclusion about the relative efficacy of CPA and castration from these data. Our study offers encouraging results for CPA therapy in terms of PSA response; and disease-specific survival rates will be identified in the further steps of this trial. If PSA-progression is considered as a surrogate marker for survival;one can make a prediction that this would translate into a similar survival time in this study population as well.

CPA has dual action as a peripheral testosterone receptor blocker and as a central agent on the hypothalamus to decrease overall serum testosterone to castrate levels[26-29]. Hence, it can be regarded as the only antihormone therapy that causes complete androgen blockade as monotherapy. The effectiveness of CPA in achieving castrate testosterone levels has been well-established in a recent study, which revealed that a near-castrate serum testosterone was reached on day 7 [30]. Herein, we evaluated testosterone levels in all the patients every 3 months and although lower in the castration group, no statistically significant difference was encountered. This may also be encouraging for CPA having the same therapeutic efficacy as castration. In a recent study which compared flutamide versus CPA treatments in advanced prostate cancer patients; the two monotherapy arms showed similar efficacy in terms of survival and time to progression, but a clearly more pronounced toxicity in the FLU arm[31]. Moreower, FLU has not been found superior to CPA with regard to sexual functions. In our study, the side effects and QOL in the treatment arms have not been assessed. Indeed, most of the patients were impotent from the beginning. Therefore, sexual interest was not a major concern among the patients. Nevertheless, almost all

of the patients have been affected to a degree in terms of libido and erectile functions. On the other hand, no serious advers events and no withdrawals due to toxicity were reported, which indicates CPA therapy as a safe and tolerable option.

This randomized, prospective study of CPA and castration in patients with metastatic prostate cancer has not so far revealed any significant difference in progression-free survival. The study is not mature, however, so the survival endpoints have not been met. The study is ongoing. Nevertheless, we think that the follow-up period has been sufficient for us to draw the following conclusion: the initial efficacy and tolerability benefit of monotherapy leads us to indicate that this therapy is safe and acceptable. So, less agressive endocrine management methods may also be considered in this subject.

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