

## BENEFITS OF INTERMITTENT/CONTINUOUS ANDROGEN DEPRIVATION IN PATIENTS WITH ADVANCED PROSTATE CANCER

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### Abstract

**Background and aims.** In 1941 Huggins described the effect of castration on prostate cancer: gonadotropin-releasing hormone (GNRH) analogues were introduced in 1985. Complete androgen blockade (association of GNRH analogue with antiandrogen) was introduced by Fernand Labrie to achieve suppression of suprarenal testosterone. Long time androgen deprivation lead to androgen independence of the prostate cancer cell.

Our principal aim was to demonstrate longer survival rates on prostate cancer patients with intermittent androgen deprivation.

### Methods:

- 82 patients in the Urology Department of Vasile Goldis West University Arad were included into two groups, with continuous and intermittent androgen deprivation.
- Treatment efficiency was assessed by the level of testosterone and PSA.
- Adverse events (AE) and serious adverse events were reported according to Common Terminology Criteria of Adverse Events (CTCAE) of the National Cancer Institute (NCI).

### Results:

- Evolution towards castrate resistant prostate cancer: 12.5% from the intermittent androgen deprivation group and 23.8% from the continuous androgen deprivation group
- Mortality rate: 15% of patients from the intermittent androgen deprivation group; 19% of patients from the continuous androgen deprivation group

### Conclusions:

1. Better quality of life (Qol) in periods without treatment due to testosterone recovery;
2. Less AE's and metabolic syndrome (MS) related complications;
3. Better survival and longer time of disease control and
4. Cost reduction.

**Keywords:** androgen deprivation, GNRH antagonist, Qol

### Background and aims

In 1941 Huggins described the effect of castration on prostate cancer (PC) [1]. Orchiectomy or estrogen lifelong treatment represented treatment options until

1985 when gonadotropin-releasing hormone (GNRH) analogues were introduced. Complete androgen blockade (association of GNRH analogue with antiandrogen) was introduced by Fernand Labrie to achieve suppression of suprarenal testosterone. Long term androgen deprivation has many adverse reactions (AE) impairing quality of life (Qol). Hot flushes, loss of libido, erectile dysfunction,

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fatigue are common AE's, but more severe reactions such as high cholesterol, diabetes mellitus, loss of bone density, cognitive impairment, muscular atrophy described now as metabolic syndrome (MS) lead to cardiovascular complications and death [2,3,4].

Long time androgen deprivation led to androgen independence of the PC cell. The mechanism of developing androgen independence is complex, with gene selection and upgrading for surviving cells. Bruchowsky's hypothesis that re-exposing PC stem cell to androgen would remake the androgen dependent phenotype was demonstrated in 1990 in one study on Shionogi tumor model. The principle of intermittent androgen suppression has been applied in prostate cancer treatment [5,6].

Our principal aim was to demonstrate longer survival rates in PC patients with intermittent androgen deprivation (IAD).

Secondary objectives were to assess improvement of QoI in the periods without treatment, prolonged survival due to less cardiovascular and osteoporosis complications, disease control for longer time and cost reduction.

**Methods**

Between 2004 – 2014 PC patients were treated at the Private Medical Centre in Arad in clinical trials FE200486CS15, FE200486CS15A, FE200486CS21, FE200486CS21A, FE200486CS35, FE200486CS35A, FE200486CS18, ARD-0301-004, ARD-0301-010, Triptocare and Triptocare LT.

After completion of trials, 82 patients were enrolled at the Urology Department of Vasile Goldis West University Arad in two groups with continuous and intermittent androgen deprivation.

The selected patients had locally advanced PC, confirmed by prostate biopsy, Gleason graded, with and without metastases. Bone scintigraphy was performed for correct TNM staging. Antiandrogen Degarelix, analogue Leuprolid, Eligard, Zoladex and Diphereline were used for

intermittent and continuous treatment [7,8,9,10,11].

Treatment efficiency was assessed by the level of testosterone and PSA.

The safety of androgen deprivation treatment was assessed by frequency and severity of AE's, significant modification of laboratory tests (biochemistry, hematology and urine analysis), ECG and vital signs, physical examination and weight (+/- 7% significant) [12,13].

Adverse events and serious adverse events (SAE) were reported according to Common Terminology Criteria of Adverse Events (CTCAE) of the National Cancer Institute (NCI) [12,13].

Patients on IAD had the treatment individualized according to TNM stage, Gleason score, initial PSA, PSA nadir and PSA doubling time [14,15,16].

Castration resistant PC (CRPC) was defined for patients with androgenic deprivation and T level lower than 0.2 ng/ml who had two PSA rising >4 ng/ml at two weeks interval or had clinical evidence of disease progression [14,15,16].

**Results**

In the continuous androgen deprivation group were enrolled 42 of patients (Table I).

**Table I.** Patients with continuous androgen deprivation (CAD).

STUDY	CS15/15A	CS21/21A	CS35/35A	TOTAL
Pt. No.	16	18	8	42

- The average age = 72.5 years,
- The mean BMI = 26.7, mean weight 79.8 kg,
- 33 patients with locally advanced prostate cancer, 9 with metastasis
- The majority of patients was with Gleason score 7,
- ECOG 0 – 17 pts, 1 – 20 pts and 2 – 5 pt.

In the intermittent androgen deprivation group were included 40 of patients (Table II).

**Table II.** Patients with intermittent androgen deprivation (IAD).

STUDY	CS18	TRIPTOCARE	ARD 0310-004	CS15A/21A/35A	TOTAL
Pt. No.	4	15	12	9	40

- The mean age was 71.5 years, mean weight 78.7 kg, BMI 26,6
- 35 patients was with locally advanced prostate cancer, 5 with metastasis
- The majority of biopsy samples revealed Gleason score 7
- ECOG 0 – 15 pts, 1 – 14 pts and 2 – 1 pt.

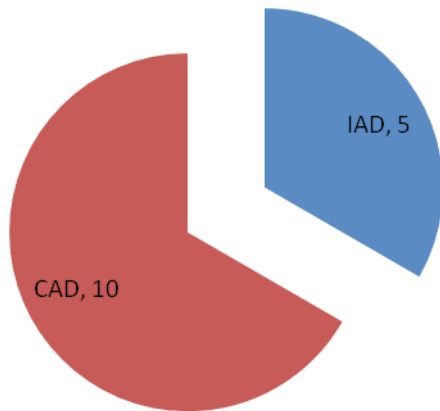
Evolution towards castrate resistant prostate cancer: 12.5% from the intermittent androgen deprivation group and 23.8% from the continues androgen deprivation group (Figure 1).

Mortality rate: 15% of patients from the intermittent androgen deprivation group; 19% of patients from the continuous androgen deprivation group (Figure 2).

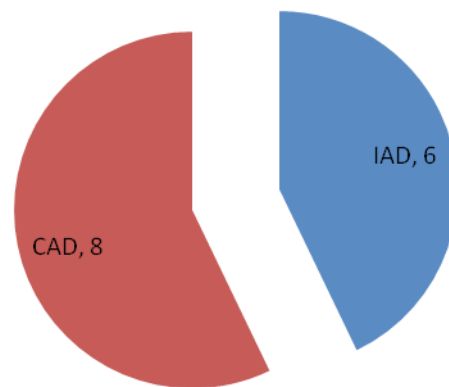
The adverse events in patients with intermittent and

continuous antiandrogenic treatment are presented below (Table III).

Lower incidence of disorders and AE's for the IAD treated patients can be explained because for 32.7% of the study period the patients were without androgen deprivation, reducing also the treatment costs. Medium time for „OFF” period was 7.8 months.



**Figure 1.** Patients with castrate resistant prostate cancer.



**Figure 2.** Dead patients.

**Table III.** Adverse events for patients with intermittent and continuous antiandrogenic treatment.

	IAD	CAD
AE's	28 (70%)	34 (80.9%)
HEMATOLOGICAL DISEASES:		
- ANEMIA	6 (15%)	11 (26.1%)
- OTHER	5 (12.5%)	9 (21.4%)
GASTROINTESTINAL DISORDERS:		
- CONSTIPATION	12 (30%)	15 (35.7%)
- DIARRHEA	11 (27.5%)	15 (35.7%)
UTI	1 (2.5%)	3 (7.1%)
METABOLIC DISEASE:		
- DIABETES MELLITUS	10 (25%)	9 (21.4%)
- WEIGHT GAIN	15 (37.5%)	25 (59.5%)
- WEIGHT LOSS	2 (5%)	2 (4.7%)
OSTEO ARTICULR DISORDERS:		
- OSTEOPOROSIS	10 (25%)	18 (42.8%)
- PAIN	3 (7.5%)	5 (11.9%)
PSYCHIATRIC DISORDERS:		
- DEPRESSION	-	1 (2.3%)
CARDIO-VASCULAR DISEASES:		
- ARTERIAL HYPERTENSION	-	1(2.3%)
- THROMBOEMBOLIC EVENTS	24 (60%)	34 (80.9%)
- HOT FLUSH	4 (10%)	3 (7.1%)
REPRODUCTIVE SYSTEM.		
- GYNECOMASTIA	1 (2,5%)	
- IMPOTENCE	20 (50%)	31 (73.8%)
CHILLS	2 (4,7%)	4 (10%)
INJECTION SITE REACTION	19 (47,5%)	30 (71.4%)
	6 (15%)	11 (26.1%)
	4 (10%)	(23.8%)

**Discussion**

Androgen withdrawal alters the ratio of stem cells in the tumor cell population. After initial reduction of tumorigenic stem cells, as the disease progresses the proportion of stem cells increased by a factor of 20 and by a factor of 500 for androgen-independent stem cells. Replacing androgen before disease progression might give rise to androgen sensitive tumor with reinduction of apoptosis, with potential of tripling the mean time to CRCP [6,17,18,19]

Results of the biggest comparative study IAD versus CAD performed by M. Hussain et al. were published in 2013. From 3040 enrolled patients 1535 were included in the study: 765 on CAD and 770 on IAD [2,9,10]

Data from the trial can be resumed as follows: in the period without treatment “OFF” QoL restored to initial level; PSA nadir dropped 95% from the initial level; first interval without treatment for patients with PSA <10, 10-20 and >20 ng/ml was 91, 65 and 39 weeks PSA at diagnosis and nadir PSA are important predictors in response and duration of the “OFF” cycle which shortens every cycle and indicates the progression to CRPC; the 4-th cycle without treatment was 23-29 weeks, without differences regarding the initial level; testosterone level rose in the “OFF” period but dropped with every cycle to 75%, 50%, 40% and 30% during cycles 1-4 of treatment. Initial PSA and “nadir” PSA levels are strong predictors of progression to CRPC [14,15,16].

**Conclusions**

Quadruple benefits were demonstrated for patients on IAD:

1. Better QoL in periods without treatment due to testosterone recovery
2. Less AE's and MS related complications
3. Better survival and longer time of disease control and
4. Cost reduction.

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