Locally advanced prostate cancer: similar therapeutic indications – what treatment to choose?

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**Abstract**

**Introduction.** Charles Dodds in 1938 synthesized dietilstilbestrol. Charles Huggins in 1941 discovered the respons of the prostate cancer to androgen supression. Andrew Shally in 1971 discovered the structure of the gonadothropine releasing hormone (GNRH). Fernand Labrie in 1981 suggested the association of the LHRH analogous with an anti-androgen (total androgen blockade - BAT). In the ‘90s Bruchovsky launched the hypothesis that the re-exposure to androgen of the prostate cancer’s stem cells would restore the androgen-dependent phenotype. This new treatment method is known as intermittent androgen supression therapy.

**Objectives:**
- The comparison of prostate cancer specific survival between the patients’ group with intermittent treatment and the another one, with continued androgen deprivation
- The evaluation of the safety and efficacy of GNRH antagonist compared with GNRH analogues.

**Materials and methods.** Between 2004 and 2014 we treated patients with prostate cancer at the Privat Medical Center Arad and they were included in several clinical trials as follows: FE200486CS15, FE200486CS15A, FE200486CS21, FE200486CS21A, FE200486CS35, FE200486CS35A, FE200486CS18, ARD-0301-004, ARD-0301-010, Triptocare and Triptocare LT. After ending the trials, 82 patients were included in a study with two branches, the first group treated with intermittent androgenic deprivation therapy, and the second group with continue androgen deprivation therapy, at the Urology Department, Western University „Vasile Goldiș“ Arad.

**Results.** Degarelix does not induce „surge“ or „micro-surge“. Degarelix reduces PSA more rapidly regardless of the disease stage. Increased efficiency and tolerability of Degarelix. All the evidence shows that there is no decrease in survival in the intermittent therapy group.

**Conclusions.** IAD improves quality of life, reduces the incidence of side effects, decreases cost and increases the duration of androgen dependency. Fewer adverse events in patients with intermittent treatment. Intermittent treatment with GnRH antagonist may become the first treatment option for most patients with prostate cancer requiring androgen deprivation. Aggressive treatment ADT / CAB during induction may increase survival.

**Keywords:** prostate cancer, ADKP, androgen deprivation therapy, Degarelix, LHRH analogous, GnRH antagonist

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**Introduction**

Charles Dodds in 1938 synthesized diethylstilbestrol. Charles Huggins in 1941 discovered the response of the prostate cancer to androgen suppression. In the same year he described the effects of the orchidectomy and estrogen (diethylstilbestrol) at patients with metastatic prostate cancer. He was the first who used systemic therapy in this disease. Andrew Shally in 1971 discovered the structure of the gonadothropine releasing hormone, Leuprolid was authorized in 1985. Patrick Walsh described in 1983 a new surgical technique, the retropubic radical prostatectomy with the preservation of the neurovascular bundle (preservation of the erectile function). Malcolm Bagshaw in 1962 investigated the possibility of the radiotherapy in the treatment of prostate cancer. Gerald Murphy evaluated the chemotherapy efficacy in hormone refractory prostate cancer. Donald Gleason created in 1966 the principal histopathological method of stadialization for prostate cancer – the Gleason score. Ming C Wang and Ming Chu discovered the prostate specific antigen (PSA) in 1979. Ming Chu got the AUA award in 1993 for the introduction of the PSA in the medical practice in USA. Fernand Labrie in 1981 suggested the association of the LHRH analogous with an antiandrogen (total androgen blockade). In the ‘90s Bruchovsky launched the hypothesis that the re-exposure to androgen of the prostate cancer’s stem cells would restore the androgen-dependent phenotype. This new treatment method is known as intermittent androgen suppression therapy.

Replacing in vivo more than a third of tumor stem cells with androgen independent stem cells represents a sufficient condition for the castrate resistant state installation. To delay the disease progression to androgen independence status the hypothesis that re-exposure of the surviving malignant cells after androgen suppression therapy to androgen, should return the cell in its normal state of differentiation, was emitted, the normal apoptotic potential returns and response to androgen deprivation reappears.

This new treatment method has been called intermittent androgen deprivation therapy. Replacing in vivo more than a third of tumor stem cells with androgen independent stem cells represents a sufficient condition for the castrate resistant state installation. To delay the disease progression to androgen independence status the hypothesis that re-exposure of the surviving malignant cells after androgen suppression therapy to androgen, should return the cell in its normal state of differentiation, was emitted, the normal apoptotic potential returns and response to androgen deprivation reappears.

This new treatment method has been called intermittent androgen suppression therapy, to patients with prostate cancer the same treatment was given.

This concept, that allows the restore of endogenous androgen level to prolong the androgen dependence period, generated pre-clinical and clinical research for intermittent androgen deprivation (IAD).

IAD provides quadruple benefits: improves quality of life in “OFF” periods of the treatment by reducing morbidity due to cardiovascular events and osteoporosis, prolongs the duration of disease response to androgen deprivation and lowers the costs. Few therapeutic changes can induce so many benefits!

**Objectives**

- The comparison of prostate cancer specific survival between the intermittent treatment group with and the continue androgen deprivation group
- The evaluation of the safety and efficacy of GnRH antagonists compared with GnRH analogues.

**Materials and methods**

Between 2004 and 2014 we treated patients with prostate cancer at the Privat Medical Centre in Arad and they were included in several clinical trials such as follows: FE200486CS15, FE200486CS15A, FE200486CS21, FE200486CS21A, FE200486CS35, FE200486CS35A, FE200486CS18, ARD-0301-004, ARD-0301-010, Triptocare and Triptocare LT. The patients received androgen deprivation treatment with GnRH antagonists: Degarelix, Teverelix and GnRH analogous: Leuprolid, Eligard, Zoladex, Diphereline and Triptoreline.

At the final of the trials, 82 patients were included in a study with two branches, the first group were treated with intermittent androgenic deprivation therapy (IAD), and the second group with continue androgen deprivation (CAD) therapy, at the Urology Clinic, Western University “Vasile Goldis” Arad.

The GnRH antagonists androgen suppression level was compared with the GnRH agonists’ (Leuprolide, Zoladex, Diphereline and Eligard) one.

**Definition of testosterone suppression:**

1. Testosterone „surge” (“flare”) = increase of T with ≥ 15% at two measurements in the first two weeks of initiation. „Flare” = clinical manifestation of the increase „surge”
2. Testosterone micro-surge = increase ≥ 25 ng/dl over the T nadir by agonist stimulation appeared after 2 weeks of treatment administration
3. „Escape” of the testosterone = at least one of T value > 50 ng/ml
4. Insufficient response T = value of the T > 100 ng/ml or two consecutive values of T > 50 ng/dl

**Teverelix** is an LHRH antagonist under investigation in clinical phase studies. It is a decapeptide with low histamine release in vitro activity similar to other

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The treatment efficacy is established with the testosterone levels obtained during the therapy with Degarelix, Teverelix, Leuprolin, Zoladex, Casodex and Triptorelin. Another important parameter was tracking of the PSA level.

Biochemical recurrence was defined when the PSA increased > 50% compared with „nadir” value and had a value over 5 ng/mL at two consecutive measurements within at least two weeks.

Classification of the adverse events was done according to the terms of common criteria for adverse events (CTCAE) of the „National Cancer Institute” (NCI).

Patients with IAD had individualized treatment based on TNM staging, Gleason score, initial PSA, PSA „nadir” and PSA doubling time.

Results

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<th>STUDY</th>
<th>CS15/15A</th>
<th>CS21/21A</th>
<th>CS35/35A</th>
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<td>8</td>
<td>42</td>
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</table>
- The mean age was 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 scor 7,
- ECOG 0 – 17 pts, 1 – 20 pts and 2 – 5 pt.

In the intermittent androgen deprivation group were included 40 of patients (Tabel II):

<table>
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<th>STUDY</th>
<th>CS18</th>
<th>TRIPTOCARE</th>
<th>ARD 0310-004</th>
<th>CS15A/21A/35A</th>
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<td>9</td>
<td>40</td>
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</table>
- 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. (Fig. 1)
Discussion

Degarelix for monthly injection was approved for PC treatment by FDA and EMEA as FIRMAGON® on 17 February 2009. Indication for antagonist androgen deprivation for patients with symptomatic metastases was introduced in EAU GUIDELINE 2010.

Definition of castration level for T was modified after analysis of results for GNRH analouges treatment and introducing chemiluminescence analysis with sensibility of 0,1 ng/ml. The T castration level is 20 ng/ml (Zlotta et al, Oefelein et al, Morote J et al) considering after castration T ≈15ng/ml (Oefelein et al).

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.

Data from the trial can be resumed as followed: in the period without treatment “OFF” Qol restore to initial level; PSA nadir drops 95% from the initial level; first interval without treatment for patients wit PSA <10, 10-20 and >20 ng/ml was 91, 65 and 39 weeks PSA at diagnosis and nadir PSA are important predictors in first interval without treatment was 23-29 weeks; without difference regarding the initial level; testosterone level rise in “OFF” period but drop with every cicle to 75%, 50%, 40% and 30% during cycles 1-4 of treatment. Initial PSA and “nadir” PSA level are strong predictors of progression to CRPC.

Advantages of IAD versus CAD were lower incidence of thrombembolic events and ginecomastia. Androgenic deprivation syndrom is modifying Qol incidence of hot flushes, loss of libido, impotence, fatigue, cognitive impairment, osteoporosis and MS are high. Lower survival rates due to cardio-vascular events are related to higer incidence of MS. The risc for osteoporosis and hip fracture can be calculated with Fracture Risk Assessment Tool (FRAX).

The strategy of IAD is in favor for the antagonist GNRH because of the rapid onset without “flare” and “surge”.

Rising of T in “OFF” periods improved Qol patients had less hot flushes, and impotence. Incidence of AE’s is higher in „ON” periods, fatigue (50,5%), dyspnea (24,8%) and hematuria (17,4%) are the most frequent. Miocardial infarction (7,3%), stroke (6,4%) and deep vein thrombosis (5,5%) decrease survival.

Most PC patients can be treated with IAD. Relapses after treatment with curative intent, patients with positive lymph nodes, even metastatic patients can be treated but only if they reach a low PSA „nadir” rapid after initiation of treatment.

The prognostic factors for IAD and disease evolution are maintenance of T< 20 ng/dl without „surge” and low PSA „nadir” level. Only patients with rapid decrease of PSA are suitable for IAD.
Conclusions

• DAI improves quality of life, reduces the incidence of side effects, decreases cost and increases the duration of androgen dependency.

• Fewer adverse events in patients with intermittent treatment.

• Intermittent treatment with GnRH antagonist may become the first treatment option for most patients with prostate cancer requiring androgen deprivation.

• Aggressive treatment ADT / CAB during induction may increase survival.

References


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