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 Goldis" 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 dietilstilbestrol. Charles Huggins in 1941 discovered the respons of the prostate cancer to androgen supression[1]. In the same year he described the effects of the orhidectomy and estrogenes (dietilstilbestrol) at the 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 conservation 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 refratory 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 antigene (PSA) in 1979. Ming Chu got the AUA award in 1993 for the introduction of the PSA in the medical practice in 1986 (USA). Fernand Labrie in 1981 suggested the association of the LHRH analogous with an antiandrogen (total androgen blockade) [2,3,4]. 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.[5,6]

Replacing in vivo more than a third of tumor stem cells with androgene 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 reexposure of the surviving malignant cells after androgene supression therapy to androgene, should return the cell in its normal state of differentiation, was emitted, the normal apoptoic 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 intermittant androgen deprivation (IAD).

IAD provides qvadruple benefits: improves quality of life in „OFF" periods of the treatment by reducing morbidity due to cardiovascular events and osteoporosis, prolonges the duration of disease response to androgen deprivation and loweres 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 androgene deprivation treatment with GNRH antagosits: Degarelix, Teverelix and GNRH analogous: Leuprolid, Eligard, Zoladex, Diphereline and Triptoreline[7,8,9,10,11].

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 androgene supression level was compared with the GNRH agonists' (Leuprolide, Zoladex, Diphereline and Eligard) one.

Definition of testosterone supression:

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 ≥25ng / 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

antagonists. Microcrystalline form teverelix LA (trifluoroacetate) exhibits increased solubility and improved pharmacokinetic and pharmacodynamic properties.

Degarelix is a drug from third generation GnRH blockers. It is in the form of a dry powder, it can be reconstituted by dissolution to obtain a suspension for subcutaneous (sc.) injection. Degarelix has reduced histamine activity in vitro and long-acting time to decrease testosterone due to the prolonged-release implant form, a gel formed spontaneously after sc injection. Degarelix is a synthetic linear decapeptide amide powder for sc. injection, the powder is obtained by drying and freezing and the active agent is an acetate dissolved in mannitol. Mannitol is used for the reconstituted product to be isotonic. Degarelix due to the physical and chemical properties is converted in the hydrogel through molecular aggregation. The gel transformation is accelerated by increasing the concentration of degarelix contact with salts and proteins. At the relevant concentrations for clinical use (between 10-60mg / ml) sc. depot formation takes place instantaneously after injection. Degarelix is reconstituted prior to injection by dissolving the powder with water by mixing gently. It is injected after complete dissolution when the solution is clear. After administration from the sc. hydrogel Degarelix is released for a long time.

The treatment efficacy was appreciated through PSA „nadir", survival period and the period upon the installation of castrate resistant prostate cancer (CRPC).

The safety of ADT treatment was appreciated by:

- Freaquency and severity of advers events (AEs)
- Significant modifications in the laboratory tests (biochemistry, hematology, and urine analysis)
- EKG and vital signs modifications
- Physical examination
- Weight (a significant modification is considered over 7%)

A group of 42 patients with prostate cancer, confirmed by biopsy, Gleason graded, locally advanced and/or metastatic, confirmed by bone-scintigraphy in treatment with CAD were compared with a group of 40 patients diagnosed with locally advanced or/and metastatic prostate cancer treated by IAD.

Clinical and demographic characteristics

For each patient were listed according to a protocol demographic descriptive statistics about history and staging of the prostate cancer, concomitent diseases and theirs medications, height, weight and body mass index.

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

Tabel I Patients with continous androgen deprivation (CAD)

STUDY	CS15/15A	CS21/21A	CS35/35A	TOTAL
Pt. Nr.	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 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):

Tabel II Patients with intermittent androgen deprivation (IAD)

STUDY	CS18	TRIPTOCARE	ARD 0310-004	CS15A/21A/35A	TOTAL
Pt. Nr.	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. (Fig. 1)

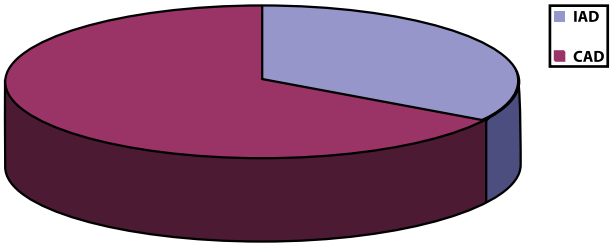


Fig. 1 Evolution towards castrate resistant prostate cancer

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

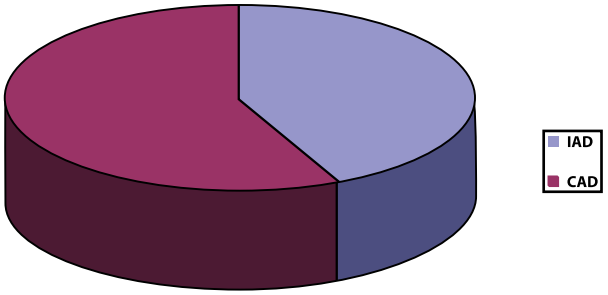


Fig. 2. Mortality rate

Lower incidence of disorders an AE's for the IAD treated patients can be explained because 32,7% from the study period the patients were without androgen deprivation, reducing also the treatment costs. Medium time for „OFF" period was 7,8 months.

Mentenance of Degarelix seric level of 9 ng/ml is sufficient to lower T at castration level. Administration of Degarelix is with initial dose of 240mg (40 mg/ml) and mentenance dose 80mg (40mg/ml) every month. Castration T level is reached in 98% of patients at day 28 and is mantained during treatment.

- 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 not a worse survival in the group treated by intermittent therapy.

Discutions

Degarelix for monthly injection was aproved for PC treatment by FDA and EMEA as FIRMAGON®. on 17 February 2009. Indication for antagonist androgen deprivation for patients with simptomatic methastases was introduced in EAU GUIDELINE 2010[8].

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/dl. The T castration level is 20 ng/dl (Zlotta et al, Oefelein et al, Morote J et al) considering after castration T ≈15ng/dl (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. [2,9,10]

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 respons and duration of the "OFF" cicle witch schortens every cicle and indicate the progresion to CRPC; the 4-th cicle without treatment was 23-29 weeks; withouth difference regarding the initial level; testosteron level rise in "OFF" period but drop with every cicle to 75%, 50%, 40% and 30% during cicles 1-4 of treatment. Initaial PSA and "nadir" PSA level are strong predictors of progresion to CRPC. [14,15,16]

Advantages of IAD versus CAD were lower incidence of thrombembolic events and ginecomastia. Androgenic deprivation sindrom is modifing 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[5].

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

1. Huggins C, Hodges CV. *Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate.* Cancer Res 1941;1:293-7.
2. Hussain M, Tangen CM, Higano C, et al. *Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group* Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984-90.
3. Keating NL, O'Malley AJ, Smith MR. *Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer.* J Clin Oncol 2006;24:4448-56.
4. Kirby R, Robertson C, Turkes A, et al. *Finasteride in association with either flutamide or goserelin as combination hormonal therapy in patients with stage MI carcinoma of the prostate gland. International Prostate Health Council (IPHC) Trial Study Group.* Prostate 1999;40:105-14.
5. Bruchovsky N, Klotz L, Crook J, et al. *Quality of life, morbidity, and mortality results of a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen relapse after radiation therapy for locally advanced prostate cancer.* Clin Genitourin Cancer 2008;6:46-52.
6. Bruchovsky N, Rennie PS, Coldman AJ, et al. *Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma.* Cancer Res 1990;50:2275-82.
7. Swanson TA, Marples B, Grills IS et al. *Effect of TMPRSS2/ERG fusion gene expression on radio- and chemo-responsiveness in prostate cancer cell lines.* Presented at: ASCO GU, CA, USA, 5-7 March 2010.
8. Sinescu I, Ioiart I, Geavlete P, Bumbu G, et. al *Ghid pentru cancerul de prostată*. Anexa nr. 10, MONITORUL OFICIAL nr. 608bis
9. Tunn U. *Can intermittent hormone therapy fulfill its promise?* Eur Urol Suppl 2008;7:752-7.
10. Tunn UW. *Intermittent endocrine therapy of prostate cancer.* Eur Urol 1996;30(Suppll):22-5;discussion 38-9.
11. Yuanshan Cui, Huantao Zong, Huilei Yan, Nan Li, Yong Zhang *Degarelix versus Goserelin plus Bicalutamide therapy for lower urinary tract symptom relief, prostate volume reduction and quality of life improvement in men with prostate cancer: a systematic review and meta-analysis,* Urol Int 2014;93:152-159
12. Klotz LH, Herr HW, Morse MJ,et al. *Intermittent endocrine therapy for advanced prostate cancer.* Cancer 1986;58:2546-50.
13. Studer UE, Whelan P, Albrecht W, et al. *Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891.* J Clin Oncol 2006;24:1868-76.
14. Catalona WJ, Bartsch G, Rittenhouse HG et al. *Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen.* J. Urol. 171(6 Pt 1), 2239-2244 (2004).
15. Catalona WJ, Partin AW, Slawin KM et al. *Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial.* JAMA 279(19), 1542-1547 (1998).
16. Cleave ME, Hsieh JT, Wu HC, et al. *Serum prostate specific antigen levels in mice bearing human prostate LNCaP tumors are determined by tumor volume and endocrine and growth factors.* Cancer Res 1992;52:1598-605.
17. Bryzgunova OE, Morozkin ES, Yarmoschuk SV, Vlassov VV, Laktionov PP. *Methylation-specific sequencing of GSTP1 gene promoter in circulating/ extracellular DNA from blood and urine of healthy donors and prostate cancer patients.* Ann. NY Acad. Sci. 1137, 222-225 (2008).
18. Calais Da Silva F, Bono A, Whelan P, et al. *Phase III study of intermittent MAB versus continuous MAB - an international cooperative study - quality of life.* Eur Urol Suppl 2006;5:289 (abs. 1066).
19. Calais Da Silva F.Goncalbes F, Santos A, etal. *Phase 3 study of intermittent monotherapy versus combined androgen deprivation.* J Urol 2006;175(4 Suppl):315 (abs. 974).