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

HORIA MURESANU
Vasile Goldis West University, Faculty of Medicine, Pharmacy and Dentistry, Arad, Romania

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
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 Qol 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 was 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 = 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.
Table III. Adverse events for patients with intermittent and continuous antiandrogenic treatment.

| Event                              | IAD     | CAD     |
|------------------------------------|---------|---------|
| HEMATOLOGICAL DISEASES:            |         |         |
| - ANEMIA                           | 28 (70%)| 34 (80.9%)|
| - OTHER                            | 6 (15%) | 11 (26.1%)|
| GASTROINTESTINAL DISORDERS:        |         |         |
| - CONSTIPATION                     | 12 (30%)| 15 (35.7%)|
| - DIARRHEA                         | 1 (2.5%)|         |
| UTI                                | 10 (25%)| 9 (21.4%) |
| METABOLIC DISEASES:                |         |         |
| - DIABETES MELLITUS                | 15 (37.5%)| 25 (59.5%)|
| - WEIGHT GAIN                      | 2 (5%)  | 2 (4.7%) |
| - WEIGHT LOSS                      | 10 (25%)| 18 (42.8%)|
| OSTEO ARTICULAR DISORDERS:         |         |         |
| - OSTEOPOROSIS                     | 20 (50%)| 32 (80%) |
| - PAIN                             | 1 (2.5%)| 1 (2.3%) |
| PSYCHIATRIC DISORDERS:             |         |         |
| - DEPRESSION                       |         | 1 (2.3%) |
| CARDIO-VASCULAR DISEASES:          |         |         |
| - ARTERIAL HYPERTENSION            | 24 (60%)| 34 (80.9%)|
| - THROMBOEMBOLIC EVENTS            | 1 (2.5%)| 4 (10%) |
| - HOT FLUSH                        | 20 (50%)| 31 (73.8%)|
| REPRODUCTIVE SYSTEM                |         |         |
| - GYNECOMASTIA                     | 2 (4.7%)| 4 (10%) |
| - IMPOTENCE                        | 19 (47.5%)| 30 (71.4%)|
| CHILLS                             | 6 (15%) | 11 (26.1%)|
| INJECTION SITE REACTION            | 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

Quaduple 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
4. Cost reduction.

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. 1941. J Urol. 2002;168(1):9-12.
2. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, 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;24:3984-3990.
3. Keating NL, O’Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24:4448-4456.
4. Kirby R, Robertson C, Turkes A, Griffiths K, Denis LJ, Boyle P, et al. Finasteride in association with either flutamide or goserelin as combination hormonal therapy in patients with stage M1 carcinoma of the prostate gland. International Prostate Health Council (IPHC) Trial Study Group. Prostate. 1999;40:105-114.
5. Bruchovsky N, Klotz L, Crook J, Phillips N, Abernach J, Goldenberg SL. 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;50:2275-2282.
7. Swanson TA, Krueger SA, Galafatos S, Tubuleanu D, Martinez AA, Wilson GD, 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, Ioia I, Geavlete P, Bumbu G, Boja R, Bucuras V. Ghid pentru cancerul de prostată –Anexa nr. 10, MONITORUL OFICIAL nr 608bis, 3 septembrie 2009.
9. Tunn U. Can intermittent hormone therapy fulfill its promise?. Eur Urol Suppl. 2008;7:752-757.
10. Tunn UW. Intermittent endocrine therapy of prostate cancer. Eur Urol. 1996;30(Suppl):22-25;discussion 38-39.
11. Cui Y, Zong H, Yan H, Li N, Zhang Y. 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, Whitmore WF Jr. Intermittent endocrine therapy for advanced prostate cancer. Cancer. 1986;58:2546-2550.
13. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, 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;24:1868-1876.
14. Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Hominger W, 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. 2004;171(6 Pt 1):2239-2244.
15. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanagan RC, Patel A, 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. 1999;279(19), 1542-1547.
16. Gleave ME, Hiehl JT, Wu HC, von Eschenbach AC, Chung LW. 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;52:1598-1605.
17. Bryazgurova 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. 2008;1137:222-225.
18. Calais Da Silva F, Bono A, Whelan P, Brausi M, Queimadelos A, Portillio J, et al. Phase III study of intermittent MAB versus continuous MAB - an international cooperative study - quality of life. Eur Urol Suppl. 2006;5:389 (abstract no. 1066).
19. Calais Da Silva F, Goncalves F, Santos A, et al. Phase 3 study of intermittent monotherapy versus combined androgen deprivation. J Urol. 2006;175(4 Suppl):315 (abstract no. 974).