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Hellenic Urology

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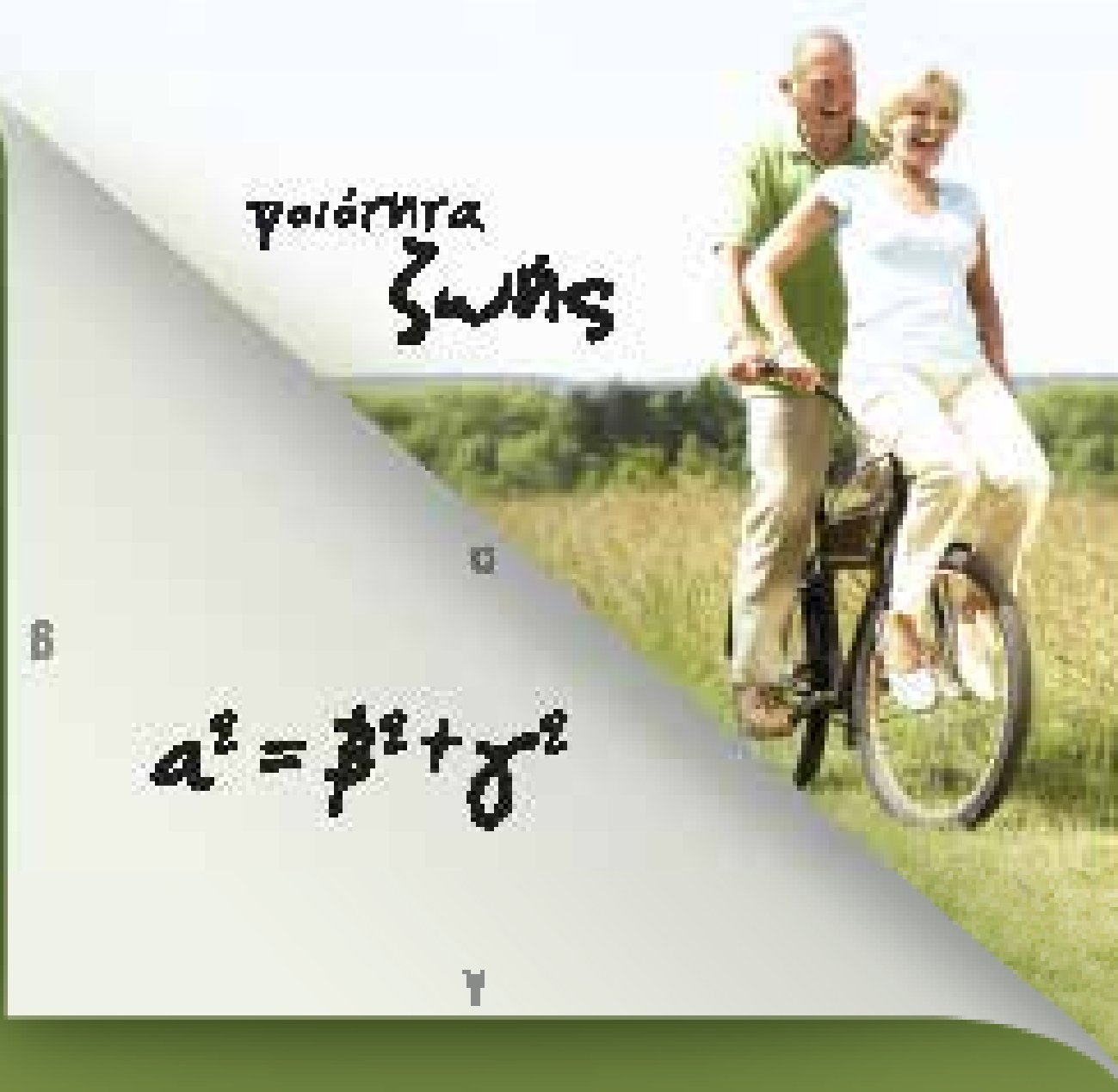
ORIGINAL ARTICLES

CASE REPORTS



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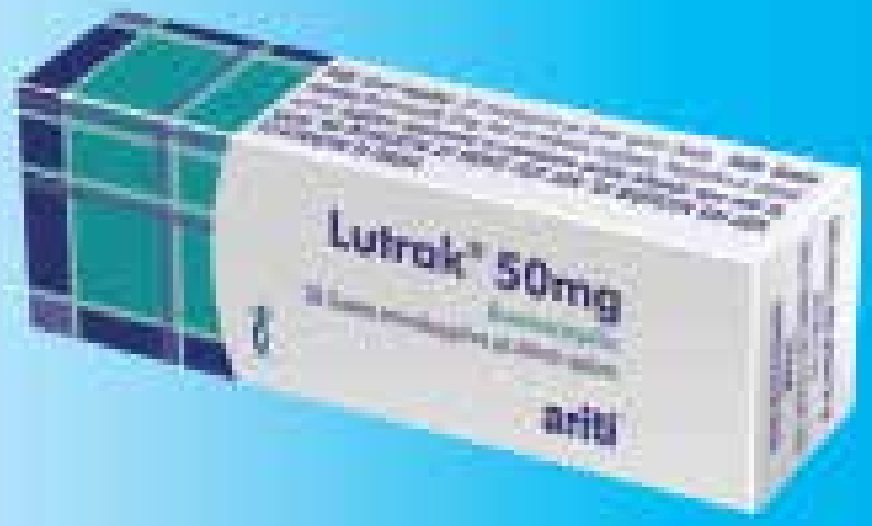

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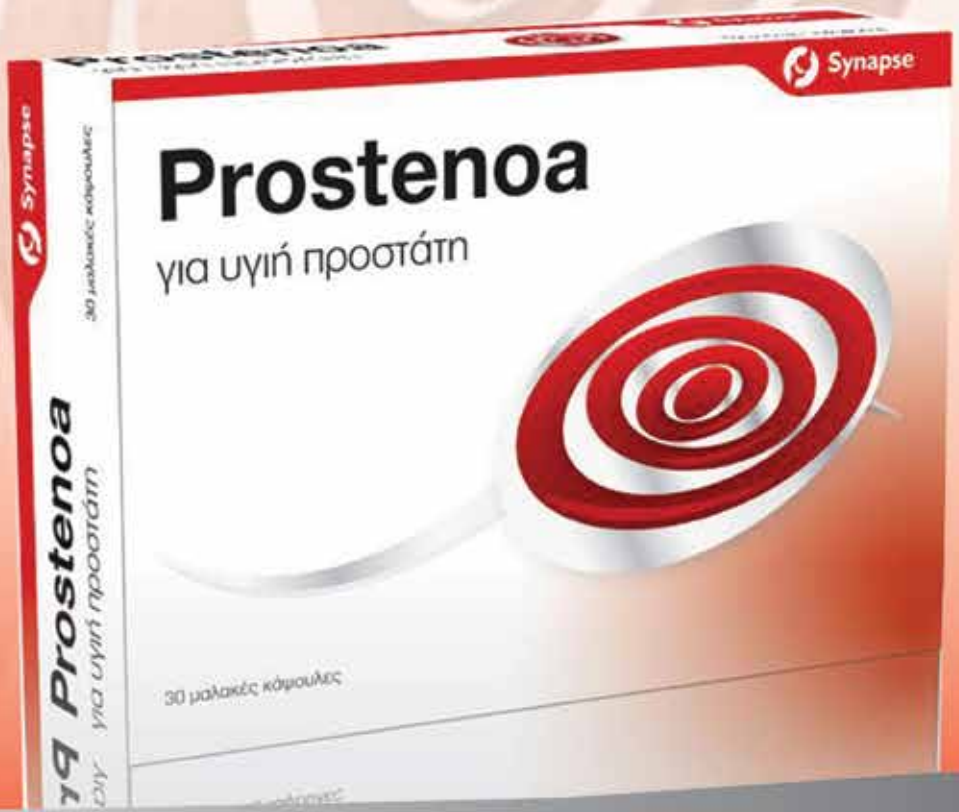

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REVIEW

Novel bone protective agents in patients with prostate cancer

Nikolaos A. Kostakopoulos, Athanasios Papatsoris
2nd Department of Urology, Medical School, University of Athens, Sismanogleio General Hospital, Greece

Abstract

Prostate cancer is the most commonly diagnosed non-cutaneous cancer and the second leading cause of cancer death in men. The tissue tropism of prostate cancer for bone coupled with the skeletal- related adverse effects of Androgen Deprivation Therapy has led to heightened awareness of SREs in castration resistant prostate cancer. In the European Association of Urology updated 2015 guidelines on the management of castration resistant prostate cancer the grade of recommendation is 'A' for offering bone protective agents to patients with bone metastases (denosumab being superior to zoledronic acid). The results of larger ongoing studies that assess the efficacy, safety and cost-effectiveness of denosumab are warranted.

Citation Kostakopoulos N, Papatsoris A. Novel bone protective agents in patients with prostate cancer. *Hellenic Urology* 2016, 28 (3): 23-29

In Castration resistant prostate cancer (CRPC) bone metastases are often present posing a substantial health and economic burden because they induce skeletal - related events (SREs: Pathological fractures, spinal cord compression, need for radiotherapy or surgery to the bone). Once bone metastases are diagnosed, the survival time varies between 12 and 55 months depending on various prognostications[1]. Clinically, bone metastases are the primary cause of morbidity and mortality for men with metastatic CRPC, with 80% - 90% of patients eventually developing metastatic disease.

Recently, the appearance of two or more new bone lesions on bone scan was included as an alternative characterization of CRPC in the guidelines of the European Association of Urology (EAU)[17]. This stresses the importance of bone protective agents for the prevention and management of skeletal - related events (SREs).

Key words
prostate cancer; castration; bone protective agents; denosumab; bisphosphonates; radium 223; abiraterone; enzalutamide

For the last two decades only intravenous (IV) bisphosphonate zoledronic acid has demonstrated efficacy in preventing SREs and has been established in the clinical practice. Recently, subcutaneous (SC) use of denosumab (a fully human monoclonal antibody of the IgG2 subtype against receptor

Corresponding author:
Dr. Athanasios Papatsoris, 1 Sismanogleiou str., Sismanogleio General Hospital, 15123 Marousi, Greece,
E - mail: agpapatsoris@yahoo.gr

- activated nuclear factor kappa - b ligand: RANKL) has gained Food & Drug Administration (FDA) approval for prevention of SREs in patients with bone metastases from solid tumors and for increasing bone mass in patients with non - metastatic PCa under androgen deprivation therapy (ADT). Furthermore, although initial ADT is uniformly effective, nearly all patients will eventually develop CRPC with bone metastases, thus the development of novel bone - targeted agents such as denosumab is more than welcomed[2].

Bisphosphonates

Bisphosphonates have been used to inhibit osteoclast - mediated bone resorption in CRPC and have proven to be highly effective in reducing bone pain. 643 patients who had CRPC[3] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal -related events (SREs) compared to the placebo group (44% *vs* 33%, *p*= 0.021) and fewer pathological fractures (13.1% *vs* 22.1%, *p*= 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL.

Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg due to toxicity. The toxicity (e.g., jaw necrosis) of these drugs, especially amino bisphosphonate, must always be kept in mind[4, 5]. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration[6]. No survival benefit has been seen in any prospective trial with bisphosphonates.

In a survey which included 200 urologists from 12 European countries including 27442 PCa patients bisphosphonates were used to the same extent in hormone-naive and castration-resistant PCa, with bone metastases, although current guidelines recommend their use only in CRPC. 78-80% of board-certified urologists prescribed BPs in both hormone sensitive PCa and CRPC[7].

RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. Denosumab binds to RANKL and prevents the maturation of osteoclasts, bone resorption and finally breaks the vicious cycle of bone destruction.

It has been developed as two products with different dosing regimens and therapeutic indications[8]. In the dose of 60 mg SC, twice yearly, it is indicated for the treatment of bone loss associated with androgen deprivation therapy (ADT) in men with prostate cancer at high risk of fracture. In the dose of 120 mg SC, every month denosumab is indicated for the prevention of SREs in patients with bone metastases from solid tumors, including prostate cancer. Several studies have been published for SRE prevention dosing regimen[8].

The results of a randomized study on 1432 men with prostate cancer that received denosumab versus placebo have demonstrated an increase in bone - metastasis - free survival[18]. In this phase III, double - blind, randomized study, denosumab significantly increased bone - metastasis - free survival by a median of 4.2 months (29.5 *vs* 25.2). In particular, the primary endpoint of the study was bone -metastasis- free survival, a composite endpoint determined by time to first occurrence of bone metastasis or death from any cause. The overall survival was similar between the two groups as well as the rate and grade of adverse effects except for hypocalcemia (2% *vs* <1%), while the jaw osteonecrosis (5% *vs* 0%) was higher in denosumab group.

These results upon the incidence and delay of SRE onset in patients with bone metastases have been confirmed by a recent meta - analysis of six controlled studies including 6,142 patients with breast cancer, prostate cancer, solid tumors except from lung cancer and myeloma[19]. Furthermore, nine (95% CI 7–11) additional people need to be treated to prevent one SRE, suggesting that this difference is clinically significant, given the morbidity and costs associated with SRE[19].

Many recent studies reported a significant superiority of denosumab versus zoledronic acid in delaying SREs and in pain and health - related quality of life[11, 12]. These studies support the early initiation of denosumab when patients present with bone metastases, including asymptomatic bone metastases, to delay SREs and the onset of worse pain or use of strong opioids[12].

A study conducted by 342 centers compared denosumab (120 mg SC) with zoledronic acid (4 mg IV) documented the prevention of SREs in 1,904 men with bone metastases from mCRPC[11]. The median time to first SRE was 20.7 months with denosumab and 17.1 months with zoledronic acid. Bone resorption markers such as urinary N - telopeptide were found to be significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p <0.0001). The rate and grade of adverse effects was similar between the two groups. The authors concluded that denosumab was more effective than zoledronic acid. Furthermore, patient - level data from three identically designed, randomized, double - blind, active - controlled, phase III studies of patients with breast cancer, prostate cancer, other solid tumors or multiple myeloma were combined[14]. Denosumab was found to be superior to zoledronic acid in delaying time to first SRE by a median 8.2 months and in reducing the risk of a first SRE by 17% (p <0.001).

The use of zoledronic acid has several limitations and inconveniences: Need for IV access and administration, monitoring of renal function, dose adjustment, on-study dose withholding and management of influenza-like syndrome. On the contrary, the aforementioned limitations do not apply to denosumab as it is administered SC, it has no effect on renal function and it is not associated with acute phase reactions[20].

Other studies showed denosumab is a cost - effective treatment option for the prevention of SREs in patients with advanced solid tumors and bone metastases compared to zoledronic acid. The overall value of denosumab is based on superior efficacy, favorable safety, and more efficient administration[16, 26].

Lastly, another recent study assessed the cost - effectiveness of denosumab vs zoledronic acid in bone - metastatic CRPC including the parameter of, quality - adjusted life - years (QALYs)[25]. Denosumab resulted in fewer estimated SREs (-0.241), more QALYs (0.0074) and lower SRE - related costs (-$2,340), but higher drug-related costs ($10,181) and total costs ($7,841) versus zoledronic acid. The base case estimated cost per QALY - gained was $1,058,741.

According to eau 2015 guidelines for "nonspecific" management of mCRPC, calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.

Cabozantinib, a Met and VEGF - R2 inhibitor was recently tested in patients with metastatic CRPC. Impressive preliminary results from a phase II study that enrolled 168 patients in 2011 were recently reported, including notably a partial or complete improvement in the bone scan in 85% and pain improvement in 60% of the patients[31]. Toxicity is as expected for a tyrosine kinase inhibitor, including fatigue, hypertension and palmar - plantar syndrome, and constitutes a challenge for the original 100 mg/day dose with respect to further development. A phase III trial was recently initiated with pain as the primary end - point and a global phase III trial with overall survival as the primary end - point in patients with metastatic CRPC failing docetaxel and abiraterone is also in the pipeline. Cabozantinib shows encouraging clinical activity in both bone and soft tissue metastatic lesions in CRPC patients and an overall disease control rate at week 12 of 74%.

Radium 223

Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone - metastatic CRPC[9, 30]. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energy close to the origin of the particle emission. Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an alpha emitter, administered intravenously requires no radiation safety precautions such as particular sleeping arrangements, limited time or specified distance from children or pregnant women. Given the excellent safety profile of Radium 223, there is interest in combination regimens with therapies such as abiraterone and enzalutamide.

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer. In the ALSYMPCA phase III placebo controlled trial 922 men with symptomatic bone - metastatic CRPC were randomized using a 2:1 ratio to receive six injections every 4 weeks

of either radium 223 (50 Kbq/kg) or placebo[9]. Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints of time to first SRE, time to alkaline phosphatase progression, alkaline - phosphatase response, alkaline - phosphatase normalization, time - to - PSA - progression, safety, and quality - of - life. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223. In addition, there was significant improvement in median time to SRE (13.6 months *vs* 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm.

Adverse events (AEs) were determined for any man who received >1 injection in 762 patients. AEs were observed in 88% of the radium 223 patients and 94% of placebo - treated patients. Serious AEs were higher in the placebo group (43% *vs* 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% *vs* 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3% *vs* 1%, thrombocytopenia 6% *vs* 2%, anemia 13% *vs* 13%). Given, that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient's oral intake and fluid status is crucial to prevent dehydration[9, 30].

Abiraterone and Enzalutamide

In the first St Gallen Advanced Prostate Cancer Consensus Conference 2015 (APCCC), which reviewed the areas of controversy in advanced prostate cancer management, the post - docetaxel use of abiraterone or both pre - and post - docetaxel use of enzalutamide, showed a significant reduction in the time to first SRE in the active treatment arms[10, 28].

Relevant studies demonstrated that abiraterone acetate had a minimal budget impact on health plans. A relevant advantage was the cost savings due to the lack of chemotherapy - related side effects as well as the ease of administration[27].

Exploratory analyses of COU - AA - 301 randomized trial, evaluating the impact of abiraterone on pain control, and skeletal - related events suggest abiraterone has efficacy in all these settings. In patients with clinically significant pain at baseline, abiraterone significantly increased the number of patients reporting palliation of pain (45% *vs* 28.8%; p= 0.0005), as well as faster palliation (median time to palliation 5.6 months *vs* 13.7 months; p= 0.0018). Median time to occurrence of first skeletal - related event (defined as pathologic fracture, spinal cord compression, or palliative surgery or radiation to bone) was also significantly longer in abiraterone treated patients (25 months versus 20.3 months; p= 0.0001)[28].

When should we initiate the bone protective agent?

In a phase III study, 645 patients with castration sensitive prostate cancer and bone metastases, where randomized with immediate initiation of zoledronic acid versus zoledronic acid initiation after disease progression into castration resistant status. In conclusion, in men with castration - sensitive prostate cancer and bone metastases, early treatment with zoledronic acid was not associated with lower risk for SREs[13].

There is still not enough evidence for the use of denosumab for patients with castration sensitive prostate cancer. Nevertheless, an exploratory analysis in a global, randomized, placebo - controlled trial of men with high - risk non metastatic CRPC showed that denosumab increases time to first bone metastasis. Patients with shorter Prostate - Specific Antigen Doubling Time (PSADT) are at greater risk for bone metastasis or death. Denosumab consistently improves bone metastases free survival (BMFS) in men with shorter PSADT and seems to have the greatest treatment effects in men at high risk for progression. In these patients denosumab increased BMFS and time to first bone metastasis. OS and overall prostate cancer progression were similar between the placebo and denosumab groups[29].

Among men with PSADT ≤10 months, time to first bone metastasis was 6.4 months longer in the denosumab group than in the placebo group (32.4 *vs* 26 months). Denosumab reduced the risk of first bone metastasis by 15% (HR, 0.85; 95% CI, 0.71 to 1.01; P = 0.065). Among men with PSADT ≤6 months, time to first bone metastasis was 4.4 months longer in the denosumab group than in the placebo group (26.5 *vs* 22.1 months). Denosumab reduced the risk of first bone metastasis by 20% (HR, 0.80; 95% CI, 0.65 to

0.97; *p*= 0.026). Among men with PSADT ≤ 4 months, time to first bone metastasis was 8 months longer in the denosumab group than in the placebo group (26.4 *vs* 18.5 months). Denosumab reduced the risk of first bone metastasis by 29% (HR, 0.71; 95% CI, 0.55 to 0.91; *p*= 0.008)[29].

Side - effects of bone protective agents

Most common early onset side - effect (first 3 days) that has been documented is a flu - like syndrome which is much more common with zoledronic acid. Hypocalcaemia, infectious side - effects and jaw necrosis are slightly commoner with denosumab[11, 14]. Osteonecrosis of the jaw (ONJ) is a serious adverse effect of denosumab administration[21]. It is a type of avascular necrosis most commonly affecting the mandible characterized of exposed, necrotic bone in the oral cavity for more than 8 weeks. As ONJ is not widely accepted to be solely avascular necrosis, direct detrimental effects of denosumab on monocytes and macrophages could provide a novel comprehensive understanding of its pathophysiology. There are data suggesting that macrophages could well be the central factor in allowing the infection of the jaw to develop first, followed by the necrosis[22]. Risk factors for ONJ include the use of a dental appliance, history of tooth extraction and less frequently poor oral hygiene[23]. ONJ responds adequately to conservative treatment and just a few patients needed surgical resection. A meta - analysis of seven randomized controlled studies demonstrated that the increased risk of ONJ was not statistically significant between denosumab and bisphosphonate treatment[21]. Before initiation of denosumab, patients should have a comprehensive dental examination. Recently, this recommendation has been added in the American Society of Clinical Oncology (ASCO) clinical practice guideline update on the role of bone - modifying agents in metastatic breast cancer[24]. Appropriate patient selection with close attention to dental health, supplementation with calcium and vitamin D are effective strategies to minimize the impact of adverse events.

Furthermore, the dosage of zoledronic acid must be based on renal function and is contraindicated when the creatinine clearance is less than 30ml/min, whereas denosumab is not excreted by the kidneys and can be administered even to patients on dialysis[15].

The most important grade 3 or higher toxicities associated with radium 223 were low myelosuppression (anemia, neutropenia, and thrombocytopenia) and low gastrointestinal rates (diarrhea, nausea, and vomiting)[9].

Conflicts of interest:

The authors declared no conflicts of interest.

Περίληψη

Ο καρκίνος του προστάτη αποτελεί τον πιο συχνά διαγνωζόμενο μη δερματικό καρκίνο και τη δεύτερη πιο συχνή αιτία θανάτου από καρκίνο στους άνδρες. Ο ιστικός τροπισμός του προστατικού καρκίνου για τα οστά σε συνδυασμό με τις σχετιζόμενες με τα οστά ανεπιθύμητες ενέργειες (SREs) της αντιανδρογονικής αγωγής, έχουν οδηγήσει σε αυξημένη προσοχή στα SREs στον ευνουχοάντοχο καρκίνο του προστάτη (CRPC). Σύμφωνα με τις πιο πρόσφατες οδηγίες της Ευρωπαικής Ουρολογικής Εταιρίας το 2015 για τη διαχείριση ασθενών με CRPC, προτείνεται με βαθμό σύστασης ¨Α¨, η προσφορά οστεοπροστατευτικών παραγόντων σε ασθενείς με οστικές μεταστάσεις (με το denosumab να υπερτερεί έναντι του ζολεδρονικού οξέος). Τα αποτελέσματα των σε εξέλιξη μελετών που επεξεργάζονται την αποτελεσματικότητα, ασφάλεια και κόστος του denosumab είναι εγγυήμενα.

Λέξεις ευρετηριασμού

καρκίνος προστάτη, οστεοπροστασία, οστεοπροστατευτικοί παράγοντες, ευνουχοαντοχή

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REVIEW

Law of Urination: All humans do not empty their bladders over the same duration

Ioannis E. Karyotis
Private Surgery Clinic, Larissa, Greece

Abstract

While parameters such as maximum flow rate, average flow rate, opening detrusor pressure, show an acceptable accuracy in indicating bladder outlet obstruction and/or detrusor dysfunction, other such as flow time are not diagnostic. In this article we discuss the issue and we theoretically demonstrate why all humans do not empty their bladders over the same duration.

Citation

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Introduction

The Hypotheses/Ideas

Urodynamic investigation is actually a functional assessment of the urinary tract that provides objective pathophysiological explanations for symptoms and dysfunctions. However, urodynamic evaluation of lower urinary tract function is not a single and physiological test. In fact it comprises a series of tests and a notable variability in reference ranges of normal urodynamic parameters exists. This fact is of great interest since appropriate treatments are decided upon urodynamic findings. While parameters such as maximum flow rate, average flow rate, opening detrusor pressure, show an acceptable accuracy in indicating bladder outlet obstruction and/or detrusor dysfunction, other such as flow time are not diagnostic. This happens because some less studied factors such as the redox status, gravity, urethral viscosity pressure, integrity of autonomous nervous system, the opening diameter of urethra, compression forces of prostate or urethral strictures, the barycenter of human body (including BMI), inertia, etc.

Key words

urology; urine flow; inertia; physics; quantum mechanics

In this article we discuss the issue and we theoretically demonstrate that all humans do not empty their bladders over the same duration.

Physics of flow

Flow is defined as the quantity of fluid (gas, liquid or vapour) that passes a point per unit time. A simple equation to represent this is Flow (F)= Quantity (Q) Time (t). Flow (thermodynamically) is sometimes defined with the equation as $\Delta Q = \Delta H - T\Delta S$ where H= Enthalpy, S=

Corresponding author:
Ioannis E. Karyotis MD, Ph.D, Urogenital surgeon,
10 Panagouli str, 41 223, Larissa, Greece, E - mail: kar20042003@yahoo.gr

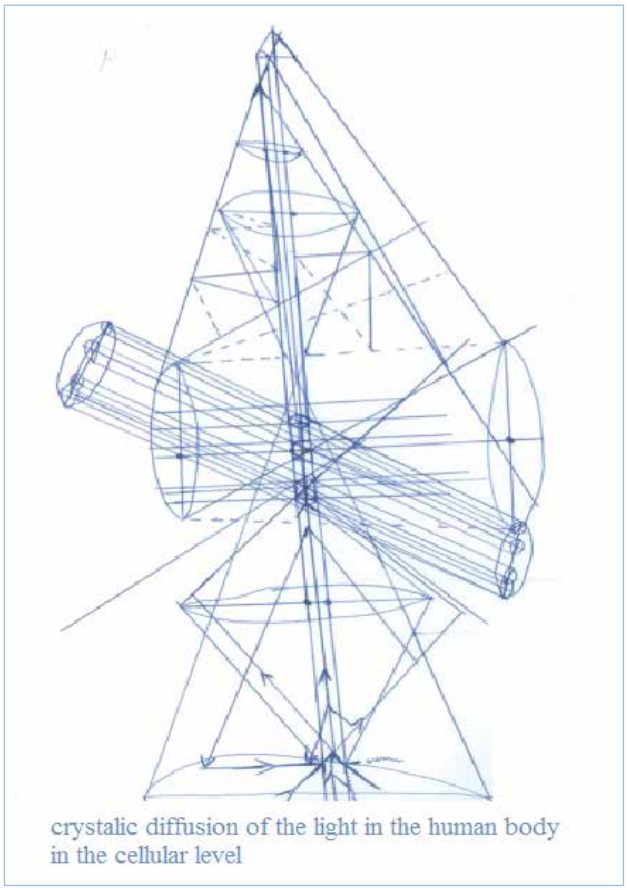

Figure 1: *Crystalloid transmission of light in human body at cell level*

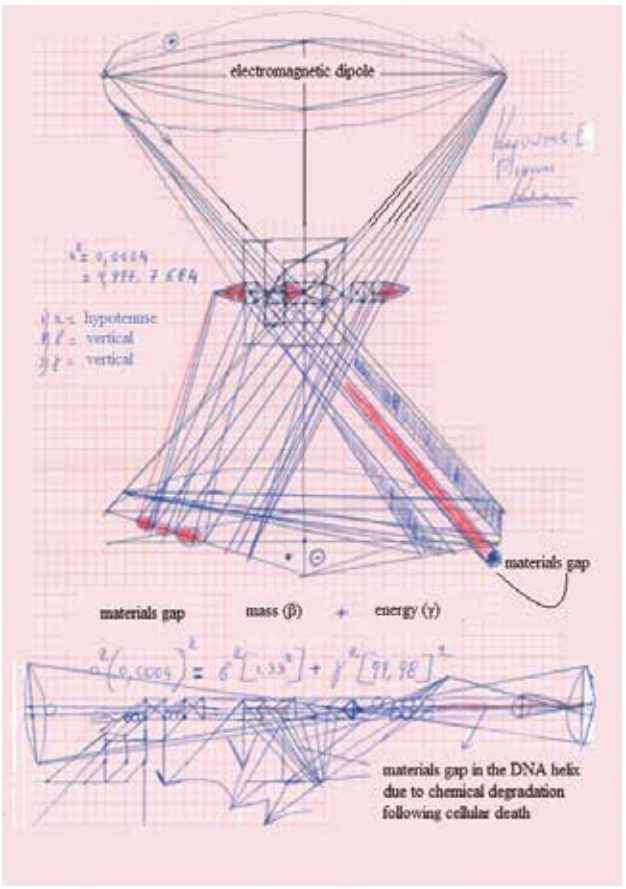

Figure 2: *Electromagnetic dipole of human body and the effect of material gap*

entropy and T= absolute temperature, or with different words, the rate of change of mass or volume or chemical reaction. Due to the number of different fluids that are given to our patients, flow is obviously an important area of physics to understand. Flow can be divided into 2 different types, laminar and turbulent. A number of different physical characteristics determine whether a fluid obeys the principles of one or the other.

In laminar flow the molecules of the fluid can be imagined to be moving in numerous "layers" or laminar. Although all the molecules are moving in straight lines they are not all uniform in their velocity. If the mean velocity of the flow is v, then the molecules at the center of the tube are moving at approximately 2v (twice the mean), whilst the molecules at the side of the tube are almost stationary. Flow is usually considered to be laminar when a fluid flows through a tube and the rate of flow is low. This is therefore the type of flow we would expect to see when a fluid floes through a cannula or a tracheal tube. For flow to occur, there must be a pressure difference (ΔP) between the ends of a tube, and it can be demonstrated that ΔQ is directly proportional to ΔP, in other words the greater the pressure difference, the greater the flow. As fluid flows through tubes there is resistance, between the fluid and urethral wall that opposes the flow. For any given system, this resistance is constant and can be expressed as: Resistance = ΔP/ΔG = R (constant). (This can be compared with V=IR in electrical physics). Urine Flow can also be Turbulent. Turbulent flow occurs when fluids flow at high velocity, in large diameter tubes and when the fluids are relatively dense. Also, decreasing the viscosity of a fluid leads to turbulent flow. The factors that determine when turbulent flow commences can be combined to form an equation which calculates the Reynolds number.

Significant statements in male human urination

- Driving forces such as gravity, bladder pressure
- Compression forces of prostatic urethra
- Thermodynamic status of male

- Stress related conditions
- Body mass index and the corresponding viscous losses within the urethra
- Quantity of urine in the bladder
- Reduction of inertia
- Anatomic related conditions.

Results

The max urine flow is closed related to process of cell death. The process of cell death is destructive, self-amplification when two basic reasons are present: a) acid PH, b) decrease of the levels of diatomic oxygen and c) decrease of the levels of water (decreased hydrolysis) inside the human body. The reasons for the above mentioned are unknown by scientists. I present in the following figures the chemical denaturation of a DNA's helix **(Figure 2)** in the human cell (based in crystalloid transmission of quantum packages of light) **(Figure 1)**. The final effect is the well-known material gap (or mass gap) and the correspondent particles are named anti-hyalo-idonia (or anti-quartzonia). These are the well known black holes, which can be viewed and in the human body (e.g. after transurethral prostatectomy) with white light. This effect is due to material gap (or effect of photonic embracing due to electromagnetic dipole), which is explained with dianysmatic logism, Euclid geometry, centroid and barycenter photonic embracing inside the body. Finally I present an equation regarding the law of male urination (mean max flow) with the following parameters.

- Redox status of human
- Gravity
- Bladder pressure
- Urethra Viscosity pressure
- Autonomous nervous system condition
- Opening diameter of urethra
- Compression forces of prostate or urethral strictures
- Barycenter of human body (including BMI).
- Starling law of bladder
- Inertia

$$\textbf{Mean max flow} = 8\,\Delta G\,(\pm 02SD)/\sqrt{32\,p\,\text{bladder}\,g^{n-1}\,L}$$

Where, ΔG = urine Flow (Thermodynamically)
P= bladder presssure
g= gravity
L= total length of urethra

This equation is predicts 95% the velocity of urine under normal conditions of normal bladder oxygenation (as well prostate and urethra) and PH status. (unpublished data).

Conflicts of interest:

The author declared no conflicts of interest.

Περίληψη

Ενώ παράμετροι όπως η μέγιστη ταχύτητα ροής, η μέση ταχύτητα ροής, η πίεση ανοίγματος του εξωστήρα, δείχνουν μια αποδεκτή ακρίβεια στην ένδειξη απόφραξης της εξόδου των ούρων απο την ουροδόχο κύστη και/ή της δυσλειτουργίας του εξωστήρα, άλλοι όπως ο χρόνος ροής, δεν είναι διαγνωστικοί. Σε αυτό το άρθρο συζητούμε το θέμα και δείχνουμε θεωρητικά γιατί όλοι οι άνθρωποι δεν κενώνουν τις κύστεις τους στην ίδια διάρκεια.

Λέξεις ευρετηριασμού

ουρολογία, ροή ούρων, αδράνεια, φυσική, κβαντομηχανική

ORIGINAL ARTICLE

The role of PCA 3 as a prognostic factor in patients with castration-resistant prostate cancer (CRPC) treated with docetaxel

Andreas Bourdoumis[1], Michael Chrisofos[2], Theodora Stasinou[3], Athanasios Papatsoris[2], Panagiotis Christopoulos[4], Athanasios Kostakopoulos[2], Charalambos Deliveliotis[2]

[1]Pennine Acute Hospitals NHS Trust, Manchester, UK

[2] 2nd Department of Urology, National and Kapodestrian University of Athens Medical School, Sismanogleio General Hospital, Athens, Greece

[3] Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust, Blackburn, UK

[4] The Christie NHS Trust, Manchester, UK

Abstract

Purpose: To investigate potential fluctuations in PCA 3 scores in castration-resistant prostate cancer (CRPC) patients treated with docetaxel and investigate the assay as a potential prognostic factor.

Materials and Methods: This was a prospective observational cohort study. Inclusion criteria included patients on hormonal treatment that were recently diagnosed with CRPC. Exclusion criteria included patients previously having radical treatment (surgery or radiotherapy) and patients who have completed the first cycle of chemotherapy. All urine samples were collected and analyzed using the Progensa® assay (Gen-Probe, San Diego, CA). Samples were collected before starting chemotherapy and at 12 months. A prospective database was created including routine blood tests, prostate staging and PSA levels throughout the study period. The effects of chemotherapy were also recorded.

Results: Between January 2010 and February 2013, 12 patients were included in the study out of an initial cohort of 23 patients with CRPC. Mean follow up was 14.8 months. Mean age at CRPC diagnosis was 73.8 years (+/-3.6 SD). Mean Gleason score was 8, with PSA 84.23 ng/ml (+/- 158 SD). Mean duration of androgen deprivation treatment was 45.16 months (+/- 34.9 SD). Mean time to castrate resistant state was 46.58 months (+/- 35.3 SD). All twelve (n=12, 100%) patients had non-assessable PCA 3 scores at baseline and at 12 months follow up. As a direct consequence, statistical analysis did not take place as the anticipated change in PCA 3 scores was not identified and correlation between measurable dif-

Key words

Castration-Resistant Prostate Cancer (CRPC); PCA 3; Androgen Deprivation Treatment (ADT); Prognostic factor; Docetaxel

Citation

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Corresponding author:

Andreas Bourdoumis, Delaunays Road, Crumpsall, Manchester, Greater Manchester, M8 5RB.

E - mail: Andreas.Bourdomis@pat.nhs.uk, bourdoua@hotmail.com

ferences was not possible. All patients tolerated chemotherapy and completed the scheduled cycles with no serious adverse effects.

Conclusion: To our knowledge, this is the first prospective study that demonstrates lack of expression of PCA3 in castration-resistant prostate cancer, with the result apparently not influenced by chemotherapy. There appears to be a strong association between hormonal treatment and lack of PCA 3 expression. It is still unknown whether disease progression per se affects PCA 3 scores. The gradual reduction and eventual complete non expression of PCA 3 with ongoing treatment and disease progression provide an insight towards molecular pathways that may be connected to castration resistant state.

Introduction

PCA3 is a segment of non-coding messenger ribonucleic acid (mRNA) from chromosome 9q21-22 and is over expressed by a median of 66 times in prostate cancer tissue relative to benign tissue[1].It is not detected in extraprostatic tissues and unlike PSA, it is not affected by age, prostate volume or other prostatic diseases (e.g. prostatitis) nor affected by PSA[2, 3]. At a cutoff score of 35, PCA 3 has a sensitivity of 64% and specificity of 76% for detecting prostate cancer and presently is used to help determine the need for repeat prostate biopsies in men who have had a previous negative biopsy[4]. Several studies have shown the superiority of PCA3 score to PSA in predicting biopsy outcome [Roobol et al. 2011]. [de la Taille et al. 2011], as increasing scores correspond frequently to a positive biopsy[5, 6]. In 2012, the US Food and Drug Administration approved PCA 3 as a diagnostic adjunct to aid clinicians in decision-making regarding repeated biopsies[7]. Furthermore, several studies have investigated the relation of PCA 3 to tumor volume and aggressiveness, with mixed results[8-10]. A pooled analysis of two multi-center European trials that evaluated the significance of PCA 3 in predicting biopsy and prostatectomy specimen characteristics by van Poppel et al showed a relationship of higher PCA 3 scores with more significant cancers with respect to indolent ones. The authors conclude that PCA 3 should be included in the decision making process for active surveillance[11].

Overall, there is a large body of evidence to substantiate the integration of PCA 3 in risk stratification models for prostate cancer diagnosis[12]. However, to this day, very little is known about the usefulness of PCA 3 as a marker of treatment response and its role in advanced disease. In this article we present our study of PCA 3 in a population of patients with advanced prostatic malignancy, aiming to identify any correlation with disease progression and treatment response.

Purpose

The primary end point of our study was to investigate potential fluctuations in PCA 3 scores in patients with castration-resistant prostate cancer (CRPC) treated with docetaxel and investigate the assay as a potential prognostic factor. Secondary outcome measures included correlation of PCA 3 with laboratory and cancer staging parameters in disease progression during chemotherapy.

Materials and Methods

This was a prospective observational cohort study, conducted in compliance with all relevant institutional, scientific and ethical committee review boards and local regulatory requirements. Informed consent was obtained from all patients. Inclusion criteria included adult patients diagnosed with locally advanced or metastatic prostate cancer (T3) who have not had any treatment other than androgen deprivation therapy (ADT), recently diagnosed with castration-resistant prostate cancer, as defined in **Table 1**, who were suitable for chemotherapy with docetaxel. Other inclusion criteria were ECOG score less than 2 and expected survival of more than 12 months. Exclusion criteria included patients previously having radical treatment (surgery or radiotherapy) and patients who have completed the first cycle of chemotherapy, as well as patients with other concomitant malignancy (urological extraprostatic, skin, liver, lung, gastrointestinal tract, brain, muskuloskeletal). Patients were recruited from the existing pool of follow up appointments at our academic centre. All patients underwent DRE and prostatic massage to obtain urine samples that were collected

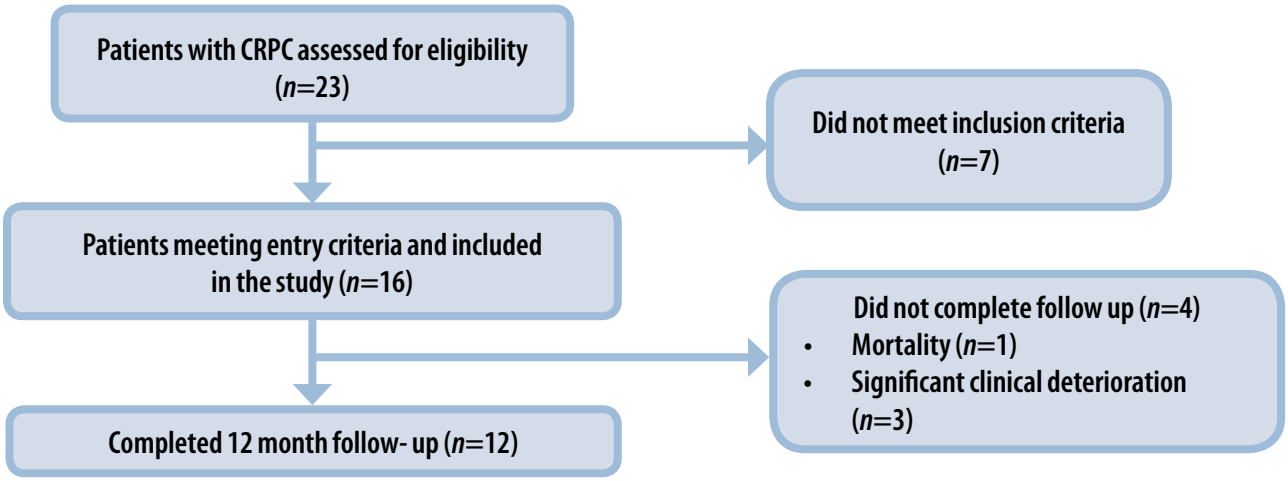

Figure 1. *Process of patient selection into the study*

TABLE 1 ***Criteria for definition of Castation Resistant Prostate Cancer (CRPC)***

Castrate serum testosterone < 50 ng/ml (1.7 nmol/L) plus either:
Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL. *or* Radiological progression: The appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours)

and analyzed using the Progensa® assay (Gen-Probe, San Diego, CA) at baseline (i.e. before starting chemotherapy) and at 12 months. PCA 3 scores were calculated as 1,000 x (PCA 3 m RNA copies/PSA m RNA copies) and all the samples were processed in the same accredited laboratory (Genekor SA ®). A PCA 3 score cut-off of 35 was determined as diagnostically significant. Non-assessable or non- informative PCA 3 results were also considered. Baseline routine blood function tests and biochemistry, PSA and PSA ratio, prostate volume (assessed by TRUS), prostate cancer diagnosis and staging information (initial biopsy PSA and Gleason score, nodal status and evidence of visceral and bone metastases), as well as duration of androgen deprivation and side effects of chemotherapy were collected on presentation and included in a prospective database, that was updated at 12 months follow up.

Docetaxel chemotherapy was administered as the standard regimen of intravenous 75 mg/m2 three weekly along with prednisolone 10 mg/day. Up to 10 cycles of treatment were planned. Dose reduction was offered to patients with serious neutropenia and/or sepsis, along with granulocyte colony-stimulating factor. Adverse effects and additional management were recorded.

For statistical analysis, a repeated measure ANOVA test was selected in order to correlate PCA 3 values pre- and post chemotherapy, and also with variables that prognosticate disease response to treatment (i.e. post chemotherapy PSA, extent of visceral and bone metastases and worsening of symptoms). Level of statistical significance was considered as $p< 0.05$.

Results

Between January 2010 and February 2013, a total of 23 patients were identified with CRPC. Of those, 16 patients met the inclusion criteria and were originally included in the study. During the initial follow up period one patient unfortunately passed away and three more deteriorated significantly and could not continue on the study. The remainder 12 patients that met the inclusion criteria completed the initial 12 months and were followed up until disease progression (**Figure 1**). Mean age at CRPC diagnosis and inclusion in the study was 73.8 years (+/- 3.6 SD). Mean Gleason score at initial diagnosis was 8, with mean PSA 84.23 ng/ml (+/- 158 SD). Androgen deprivation treatment consisted of LHRH agonist (8 patients Goserelin acetate, 5 patients Leuprorelin acetate, 3 patients Triptorelin) in combination with a non-steroidal antiandrogen for the first four weeks in all patients. Mean duration of androgen

TABLE 2 *Results of the major study parameters per patient and mean values*

PATIENT (S/N)	AGE (YEARS)	TIME TO CRPC SINCE DX (MONTHS)	PSA AT DX	GLEASON SCORE	STAGE (TNM)	ADT DURATION (MONTHS)	PSA AT CRPC	PCA 3 AT BASELINE	PCA 3 AT 12 MONTHS	PSA AT 12 MONTHS	FOLLOW-UP (MONTHS)
1	71	47	34	7	T3N0M0	48	33.8	Not assessable *	Not assessable *	14.28	17
2	77	30	24.1	8	T4N1M1b	26	691	Not assessable *	Not assessable *	60	19
3	74	6	5000	9	T3N1M1b	6	482	Not assessable *	Not assessable *	1,086	12
4	78	10	5.5	9	T4N1M0	9	832	Not assessable *	Not assessable *	58	18
5	75	89	21.9	8	T3N0M0	87	54	Not assessable *	Not assessable *	376	18
6	70	91	8.7	8	T3N0M0	89	89	Not assessable *	Not assessable *	71	14
7	69	25	4.1	7	T3N0M0	24	1.84	Not assessable *	Not assessable *	18.96	14
8	72	108	19.1	7	T3N0M0	106	27.09	Not assessable *	Not assessable *	32.86	16
9	73	24	12.4	8	T3N0M0	23	19.1	Not assessable *	Not assessable *	92.4	12
10	80	76	12	8	T3N0M0	74	12.33	Not assessable *	Not assessable *	42.31	12
11	77	15	324	9	T4N1M1b	14	426	Not assessable *	Not assessable *	286.3	12
12	70	38	45	8	T3N0M0	36	98	Not assessable *	Not assessable *	45.73	14
Mean	73.8	46.58	84.23	8	-	45.16	230.51	-	-	181.98	14.8

** Non assessable: PSA m RNA < 7500 copies/ml.*

CRPC: Castration Resistant Prostate Cancer, Dx:Diagnosis

deprivation treatment was 45.16 months (+/- 34.9 SD). Mean time to castrate resistant state from original diagnosis was 46.58 months (+/- 35.3 SD). Mean PSA at CRPC diagnosis was 230.51 ng/ml (+/- 296.75 SD), with free PSA 58.6 ng/ml (+/- 90.3 SD) and PSA ratio 0.26 +/- 0, 11 SD. Mean prostate volume as measured by transrectal ultrasound was 40.1 cc (+/- 17.6 SD). Mean ECOG score was 1. Mean overall follow up was 14.8 months. Post chemotherapy PSA at 12 months follow up was 181,98 ng/ml +/- 306.2 SD, free PSA 66.55 ng/ml +/- 142.0 SD and PSA ratio 0.34 +/- 0.1 SD. A summary of the results is provided in **Table 2.**

All twelve (*n*=12, 100%) patients had non-assessable PCA 3 scores at baseline and at 12 months follow up. Of note, baseline PCA 3 was non assessable due to PSA m RNA levels below the level of detection in all sixteen (*n*=16) patients at baseline. As a direct consequence, statistical analysis did not take place as the anticipated change in PCA 3 scores was not identified and correlation between measurable differences was not possible. Integration of a time-to-event model was also not possible again because there was no measurable difference to begin with.

All patients tolerated chemotherapy well for the first three months, with no adverse effects, and bone pain improved significantly. In the following cycles, one patient experienced neutropenic sepsis that was successfully treated, three patients experienced low-grade fever, malaise and anorexia, which did not alter treatment and two patients experienced anorexia, diarrhea and vomiting. All patients completed the scheduled treatment cycles with significantly improved symptoms and no new metastases during the study follow-up period.

Discussion

Early efforts to identify the influence of medical intervention on PCA 3 scores have produced equivo-

cal results. In their pilot study, Van Gils et al. investigated the effect of dutasteride on the PCA3 score, to find a variable and unpredictable response, albeit in a small, mixed cohort of patients with BPH and localized prostate cancer[13].The only other study to date that investigates the prospective role of PCA 3 as a prognostic marker for advanced disease and treatment response is the Triptocare study. It consists of a prospective, open-label, multicentre, single arm phase 3 study of triptorelin 22.5 mg in men with locally advanced and/or metastatic disease who were previously naive to ADT and results were recently published[14]. The study assessed PCA 3 and TMPRSSG-ERG scores at baseline and after 1, 2 and 6 months of treatment with triptorelin. In a population of 322 patients, 39 (12.1%) had non-assessable PCA3 at baseline. The frequency of non-assessable PCA 3 increased with time on androgen deprivation, namely 109 patients at 1 month (33.9%), 215 patients (68.7%) at 3 months and 232 patients (77.9%) at 6 months of treatment. Of great interest is the finding of the proportion of hormone naive individuals who never expressed PCA 3 at baseline (*n*=39, 12.1%). This subgroup was not investigated further, however, as it was not part of the initial objective. As the majority of these patients had a Gleason score of equal or greater than 8, the paucity of PCA 3 detection could be attributed to higher grade and/or more advanced disease. In their assessment of PCA 3 expression in radical prostatectomy specimens, Robert et al. have demonstrated lower PCA 3 scores in high grade cancers[15]. Furthermore, high Gleason score at baseline was the only factor significantly correlated to non-assessability of PCA 3 at 6 months in the Triptocare study[14]. On the other hand, the investigators also point out that in the remainder of the study group, lower PCA 3 scores expression correlated significantly with higher baseline PSA values (> 200 ng/ml). This is somewhat contradictory, as it was shown in the early research by Partin et that patients with advanced disease and higher grade and volume tumors are more likely to produce less PSA per gram tissue as a consequence of decreased differentiation[16].

The disruption of prostatic architecture in higher grade tumors has also been postulated as explanation for low PCA 3 scores. The loss of glandular pattern in higher Gleason score cancer leads to obliteration of the ducts and lumen, making it difficult to express prostatic cells in the urine in order to achieve a measurable result [7]. Histopathologic changes in hormonally treated prostate cancer cells are mainly characterized by cellular shrinkage with little cytoplasm, that translates to glandular shrinkage and an overall reduction in size. DRE in these patients often reveals a small, hard prostate. However, this hypothesis is contradicted by the fact that, although PCA 3 was not assessable, prostate cells were identified in the urine of all patients in our study, suggesting a molecular rather than a mechanical mechanism.

According to our findings, another possible mechanism would be an ablative effect of androgen deprivation to PCA 3 expression, something also shown in the Triptocare study. Continuation of ADT in CRPC patients throughout the chemotherapeutic period constitutes common practice and probably relates better to our results than any effect of docetaxel treatment. In our study, PCA 3 was non assessable both at baseline and at 12 months follow up after the completion of chemotherapy. Based on the above findings, further research is required to answer the questions of the true nature of PCA 3 m RNA in prostate cancer molecular pathogenesis pathways and its expression during the various stages of progression. The Triptocare investigators point out in addition that hormone naive patients with metastases produced significantly lower PCA 3 scores than men without metastases[14]. In our study of exclusively metastatic patients, non-assessable PCA 3 was the rule, which substantiates further the hypothesis of declining PCA 3 expression with ADT and advancing disease.

In both studies, PCA 3 failed to prove as a marker for disease prognostication and treatment response. Nevertheless, paucity of PCA 3 expression with ADT has never been demonstrated previously and this discovery may have yet to reveal its full potential. In retrospect, the evident gradual decrease in PCA 3 detection with ongoing ADT and the eventual complete non-assessability demonstrated in our cohort appear to be sequential events. The EFFECT trial is another prospective open label single arm multicentre trial that is currently ongoing and investigates the effect of leuprorelin acetate at 6 months on PSA, PCA 3 and TMPRSS2-ERG-mRNA amongst other markers. In our cohort, 8 patients received Goserelin acetate, 5 patients Leuprorelin ac-

etate, 3 patients Triptorelin previously and continued throughout chemotherapy. The trial aims to recruit 50 patients and compare testosterone and PSA with the newer biomarkers to provide more evidence and much needed answers in the field of advanced prostatic malignancy[18].

Conclusion

To our knowledge, this is the first prospective study that demonstrates lack of expression of PCA3 in castration-resistant prostate cancer, with the result apparently not influenced by chemotherapy. There appears to be a strong association between hormonal treatment and lack of PCA 3 expression, probably by means of an ablative effect to gene expression. Although preliminary evidence from other studies supports this theory, it is still unknown whether disease progression per se affects PCA 3 scores. The ongoing EFFECT trial will add to the existing evidence. The gradual reduction and eventual complete non expression of PCA 3 with ongoing treatment and disease progression provide an insight towards molecular pathways that may be connected to events leading to castration resistant state.

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Conflicts of interest

The authors declared no conflicts of interest.

Περίληψη

Ο πρωταρχικός σκοπός της μελέτης ήταν η ανεύρεση διακυμάνσεων του αθροίσματος του PCA 3 σε ασθενείς με προχωρημένη νόσο που μόλις μετέπεσαν σε ορμονοαντοχή και υπεβλήθησαν σε αγωγή με δοσιταξέλη (docetaxel) και η πιθανή προγνωστική σημασία. Όλοι οι ασθενείς υπεβλήθησαν σε δακτυλική εξέταση και προστατική μάλλαξη ώστε να γίνει συλλογή δείγματος ούρων κατάλληλο για επεξεργασία και ανάλυση επιπέδων PCA 3 με τη χρήση του αντιδραστηρίου Progensa assay σύμφωνα με τις προδιαγραφές της κατασκευάστριας εταιρείας (Gen-Probe, San Diego, CA, USA) κατά την ένταξη στη μελέτη και μετά από πάροδο 12 μηνών υπό χημειοθεραπεία. Συντάχτηκε έτσι μια προοπτική βάση δεδομένων που συμπεριλάμβανε το είδος και τη διάρκεια θεραπείας ορμονοαποκλεισμού καθώς και τις παρενέργειες των θεραπευτικών σχημάτων καθ'όλη τη διάρκεια της μελέτης.

Το συνολό των ασθενών (*n*=12, 100%) παρουσίασε μη ανιχνεύσημο άθροισμα PCA 3, τόσο στην αρχή όσο και στο τέλος της μελέτης. Το χημειοθεραπευτικό θεραπευτικό σχήμα έγινε καλά ανεκτό από τη πλειοψηφία των ασθενών κατά το πρώτο τρίμηνο, χωρίς την εμφάνιση ανεπιθύμητων παρενεργειών και με βελτίωση του οστικού άλγους σε ασθενείς με μεταστάσεις.

Η μελέτη μας αποτελεί τη πρώτη και μοναδική αναφορά στην ανεύρεση και το ρόλο του PCA 3 σε ασθενείς με ορμονοάντοχο καρκίνο του προστάτη, και μετά από χημειοθεραπεία. Φαίνεται να υπάρχει μια καλή συσχέτιση μεταξύ της μη ανίχνευσης αθροίσματος PCA 3 και ορμονοθεραπείας, πιθανώς μέσω μιας μοριακής οδού που επιφέρει αναστολή έκφρασης του αντίστοιχου γονιδίου. Έμμεσα, ένα τέτοιο εύρημα θα μπορούσε να χρησιμοποιηθεί για τον νωρίτερο εντοπισμό ασθενών που εμπίπτουν σε ορμονοαντοχή.

Λέξεις ευρετηριασμού

ευνουχοάντοχος καρκίνος ρροστάτη (CRPC), PCA 3, Θεραπεία ορμονοαποκλεισμού (ADT), προγνωστκός παράγοντας, δοσιταξέλη

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ORIGINAL ARTICLE

Laparoscopic nephrectomy: Primary results of two years experience in our center

Konstantinos Skriapas[1], Zacharias Chousianitis[1], Konstantinos Galanoulis[1], Eleftherios Tsiakoulias[1], Dimitrios Danieliants[1], Evangelos Alexiou[2]
Department of Urology, General Hospital of Larisa, Larisa, Greece
Department of Radiology, General Hospital of Larisa, Larisa, Greece

Abstract

Objective: To describe our initial experience with laparoscopic renal surgery (LRS) and to evaluate the efficacy and the safety of the procedures.
Methods: A retrospective review of our records revealed 19 patients (16 for nephrectomy and 3 for nephroureterectomy) who underwent LRS in our institution during the last 2 years. Transperitoneal approach was preferred using 3 trocars. Ages, gender, indications for surgery, operative time, conversion rates, blood loss, intraoperative and postoperative complications were analyzed and evaluated. Histological results and outpatient follow-up were also recorded.
Results: 11 patients were male and 8 patients female with median age of 64.5 (42-75). One procedure (nephroureterectomy) was converted to open surgery. In twelve patients histological examination revealed renal cell carcinoma (pT1-T2b), no functional kidneys in four patients and in T1G3-T3G3 disease in three patients. No major perioperative or postoperative complications were noticed. The mean (range) operative duration was 169 (128-247) minutes while the mean intraoperative blood loss was 136 (70-350) ml. The average hospital stay was 3.6 days while the mean follow up is 14 (2-21) months.
Conclusions: LRS may be currently considered safe and effective procedure associated with minimal morbidity. Due to faster recovery and improved cosmetic results, the laparoscopic approach has become the standard approach for the treatment of upper urinary tract diseases in our institution.

Key words
laparoscopic nephrectomy; radical nephrectomy; nephroureterectomy

Citation
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Corresponding author:
Konstantinos Skriapas MD, PhD, FEBU, Department of Urology, General Hospital of Larisa, Tsakalof 1, 41221, Tel. 2414504265, Mob. 6945493816, E - mail: Kostas.skriapas@hotmail.com

Introduction

First described from Clayman et al in 1991[1], laparoscopic nephrectomy (LN) raised tremendous interest as a new surgical approach for kidney diseases while the procedure has gained worldwide acceptance and popularity. Back in 1998, Rassweiler et al reported that in Germany, only 8% of the laparoscopic procedures were performed for malignancy[2]. Since then, the indications have been extended from simple nephrectomy for benign disease to radical nephrectomy and nepfroureterectomy due to malignancy. Laparoscopic renal surgery (LRS) has proven to be oncologically safe even to open nephrectomy[3-5], providing simultaneously significant benefits in terms of blood loss, postoperative pain, cosmetic results and faster recovery time[6-9]. Considering that over the past decade technical developments have improved various aspects of the procedure, nowadays most of the urologic procedures especially for malignancy have been performed laparoscopicaly and this can be confirmed by the increasing number of articles published worldwide.

The aim of this study is to present our initial experience and patients' outcome after nineteen laparoscopic procedures in our clinic during the last twenty months.

Materials and methods

We performed a retrospectively review of our medical records, between January 2014 and October 2015 seeking for patients who underwent laparoscopic procedures for diseases of the upper urinary tract either benign or malignant.

Exclusion criteria were patients with tumors greater than cT2a stage, and presence of renal abscess or severe perinephric inflammation. Patients eligible for partial nephrectomy (with tumors ≤ 4 cm) underwent open partial nephrectomy. Furthermore, lymphadenectomy was not carried out as a routine hence; patients with lymph node enlargement were excluded from the study. In order to determine the tumor size the renal vasculature all patients underwent contrast enhanced computed tomography and digital elective angiography at the same time.

Nineteen patients that underwent laparoscopic procedures for upper urinary tract diseases were identified. The first seventeen procedures were performed by one surgeon (K.S.), while the latter two from another (Z.CH.). Subjects were informed before the procedure about the possible complications and they signed an inform consent. All the procedures were performed under general anesthesia without regional anesthesia. Postoperative pain was treated with oral painkillers. Patients were placed in flank position, without modifications on the operating table and transperitoneal approach was followed using three trocars. Using the Hasson technique, the first trocar (10mm) was placed lateral to the umbilicus, while the second (Versaport plus RPF 5 - 10 - 15mm) and the third (5mm) working trocars were placed under direct visualization lateral to the rectus muscle at the level of umbilicus (near to the iliac crest) and below the costal margin in the midclavicular line respectively[10]. For the ligation of the big renal vessels Hem - o - lock clips were used, while colon mobilization, laparoscopic dissection and hemostasis were accomplished using Harmonic energy. Specimens were removed intact and entrapped in a non - permeable self opening bag (Endocatch 15mm), through an incision in the left or right lower abdominal quadrant. We determined the time of the procedure from the first incision until the exit of the surgical preparation.

Results

Between January 2014 and October 2015 nineteen laparoscopic procedures for upper urinary tract diseases were performed in our clinic. Among the nineteen cases sixteen patients underwent LN, four due to non functional kidneys and twelve due to renal tumor, and three patients underwent laparoscopic nephroureterectomy (LNU), due to tumor in the renal pelvis or the ureter. **Table 1** shows patients and tumor characteristics.

One LNU was converted to open procedure because of the poor progression of the laparoscopic procedure. In the other two nephroureterectomies, bladder cuff excision was accomplished in the first one extravesically with a Gibson incision because the tumor was in the ureter, while in the other one, a transurethral resection of the orifice and intramural ureteral was performed prior to the LNU.

There were no major postoperative complications and no perioperative or postoperative mortality. In the fourth case we tried to use a vascular stapler

TABLE 1	*Patients and tumor characteristics*	
	LN	LNU
Number of pts	16	3
GENDER Male Female	 11 5	 3
Age (years)	61	64
TUMOR LATERALITY Right Left	 4 12	 1 2
Tumor stage T1b T2a T2b	 4 5 3	 2×T1 G3 (pelvis) T1 G3 (ureter)

but this was malfunctioning thus we used again Hem - o - lock clips. There are no absorbable, single loads, multiple use clips and we found that are a cheap solution easy to use. In patients with renal tumors surgical margins were negative. The mean (range) operative duration was 169 (128 - 247) minutes while the mean intraoperative blood loss was 136 (70 - 350) ml. No patient required blood transfusion postoperatively and no wound related complications were recorded in any patient. The average hospital stay was 3.6 days while the mean follow up is 14 (2 - 21) months.

Discussion

For several years the standards of care for the treatment of renal tumors was open nephrectomy or open nepfhroureterectomy. Since the first report of the laparoscopic nephrectomy[1], renal surgery has undergone significant changes over the past fifteen years. Solid evidence, supporting oncological efficacy comparable to open procedures, is available nowadays and the laparoscopic approach has become, gradually, the standard of care in upper urinary tract diseases[11, 12]. Considering that the number of publishing papers worldwide for laparoscopic procedures is enormous, seems that during the last decade laparoscopic renal surgery has become the most frequent procedure performed by urologists.

Laparoscopic procedures especially LN can be performed by the transperitoneal or retroperitoneal approach[10]. Both methods gained popularity and they have advantages and disadvantages. In our clinic we started with transperitoneal approach and we are still continuing because we believe that we have the possibility to perform more maneuvers or to use more trocars if that is needed. Considering that no studies have shown clear advantage of one approach over the other, we strongly believe that it depends from the surgeon what approach is going to use and this is advantageous for the surgeon and the patient. In addition, the safety of LNU has been demonstrated and many retrospective studies reported that open and laparoscopic access has equivalent efficacy in T1 - T2/N0 tumours[13 - 15]. Unfortunately, because urothelial carcinomas of the upper urinary tract are rare, there is lack of prospective trials and to the best of our knowledge only one prospective randomized study has shown that LNU is not inferior to open for non - invasive upper tract urothelial carcinoma[16].

Furthermore, there is no consensus as to the optimal technique to excise bladder cuff and several techniques for bladder cuff excision are acceptable[17]. One of the most utilized approaches is the open method which allows to the surgeon to control the distal ureter and bladder cuff. We used this method for a patient with a tumor in distal ureter and we believe that the disadvantage of this method is the time consuming while the advantage is that the same Gibson incision is used for simultaneous intact extraction of the en - bloc specimen. Furthermore, because the ureter is clipped at the beginning of the procedure we minimizing the risk of tumor spillage. On the other hand, we used transurethral resection of the bladder cuff in a patient with tumor located in the renal pelvis. We found this method easy, save and bloodless. Abou El Fettouh et al., in a large multicenter American and European study, reported that the local recurrence rates and the development of metastases depended on pathologic tumor stage and was irrespective of bladder cuff approach[18].

In the present study, we evaluated the outcome of our first cases of laparoscopic renal surgery. One of the limitations is that the study extended in a short time of period while the distribution of cases was somehow uneven. At the beginning of our series we performed LN only for benign diseases and gradually more dif-

ficult cases such LNU were performed. This probably might be explained from the progression of our experience. Hence nowadays, the laparoscopic approach for LN or LNU is routinely discussed with all patients' regardless obesity and previous abdominal or renal operations excluding those having tumors larger than 10 cm, severe renal inflammatory disease and tumor thrombi in renal vein. Furthermore, all the laparoscopic procedures were initially entirely performed by one surgeon with previous laparoscopic training, whereas in our later patients, another surgeon with no previous laparoscopic experience was able to perform the procedure as a part of a teaching program.

No major postoperative complications were observed in our patients. Considering that most of the patients undergoing open surgery develop late complications due to incision (paresthesias, hernia in scar, bulging related to abdominal wall weakness)[19], we strongly believe that one of the main advantages of the laparoscopic approach is to avoid these late complications. One of the main problems during the laparoscopic procedures is the operative time. In our series the operative time was constantly decreased not similar to the operating time required for open procedure but quite enough to encourage us to continue. The significant shortening in operating time was due to our progression on the learning curve and to the standardization of the procedure.

In conclusion, despite our small number of patients we believe that laparoscopic procedures are the present and at the moment the future in urology. Nowadays, with the existing data in the literature we strongly believe that especially LN can be considered as a routine procedure associated with minimal morbidity and significant advantages for the patient. Short hospitalization and equivalent ontological outcomes makes the laparoscopic approach the standard approach for nephrectomy at our institution.

Conflicts of interest

The authors declared no conflicts of interest.

Περίληψη

Σκοπός: Να περιγράψουμε την αρχική μας εμπειρία και να αξιολογήσουμε την αποτελεσματικότητα και την ασφάλεια της λαπαροσκοπικής νεφρεκτομής.
Μέθοδος: Αναδρομική μελέτη των αρχείων μας απεκάλυψε 19 ασθενείς (16 με νεφρεκτομή και 3 με νεφροουρητηρεκτομή) που υποβλήθηκαν σε λαπαροσκοπική επέμβαση στην κλινική μας κατά τη διάρκεια των τελευταίων 2 ετών. Η διαπεριτοναϊκή προσπέλαση προτιμήθηκε χρησιμοποιώντας 3 τροκάρ. Η ηλικία, το φύλο, οι ενδείξεις για την επέμβαση, ο χειρουργικός χρόνος, τα ποσοστά μετατροπής, η απώλεια αίματος, οι διεγχειρητικές και μετεγχειρητικές επιπλοκές αναλύθηκαν και αξιολογήθηκαν. Τα ιστολογικά αποτελέσματα και η μετεγχειρητική παρακολούθηση των ασθενών καταγράφηκαν επίσης.
Αποτελέσματα: 11 ασθενείς ήταν άνδρες και 8 γυναίκες με μέση ηλικία 64,5 (42 - 75). Μια επέμβαση (νεφροουρητηρεκτομή) μετατράπηκε σε ανοικτή. Σε δώδεκα ασθενείς η ιστολογική εξέταση αποκάλυψε καρκίνωμα νεφρικών κυττάρων (pT1-T2b), μη λειτουργικούς νεφρούς σε τέσσερις ασθενείς και T1G3 - T3G3 νόσο σε τρεις ασθενείς. Δεν παρατηρήθηκαν σημαντικές περιεγχειρητικές ή μετεγχειρητικές επιπλοκές. Η μέση διάρκεια της επέμβασης ήταν 169 (128 - 247) λεπτά, ενώ η μέση διεγχειρητική απώλεια αίματος ήταν 136 (70 - 350) ml. Η μέση διάρκεια παραμονής στο νοσοκομείο ήταν 3,6 ημέρες, ενώ ο μέσος όρος παρακολούθησης είναι 14 (2 - 21) μήνες.
Συμπέρασμα: Η λαπαροσκοπική επέμβαση για την εκτομή νεφρικών όγκων, μπορεί να θεωρείται σήμερα μια ασφαλής και αποτελεσματική διαδικασία που σχετίζεται με ελάχιστη νοσηρότητα. Λόγω ταχύτερης ανάρρωσης και βελτιωμένου αισθητικού αποτελέσματος, η λαπαροσκοπική προσπέλαση για νεφρικούς όγκους, έχει γίνει η καθιερωμένη προσέγγιση για τη θεραπεία του ανώτερου ουροποιητικού συστήματος στην κλινική μας.

Λέξεις ευρετηριασμού
λαπαροσκοπική νεφρεκτομή, ριζική νεφρεκτομή, νεφροουρητηρεκτομή

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ORIGINAL ARTICLE

Investigation of the factors affecting the burden on caregivers of elderly patients with urinary incontinence: A cross-sectional study in Greece

Athanasios Zachariou[1], **Maria Filiponi**[2]
[1]*Urology Department, Elpis Hospital, Volos, Greece*
[2]*Laboratory of Endocrinology and Metabolic Disorders, Department of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece*

Abstract

Purpose: Population ageing is directly associated with the occurrence of diseases related to old age, such as urinary incontinence. This does not only aggravate the quality of life of elderly patients, but is also an important element that affects the mental health and quality of life of their caregivers. The purpose of the study is to assess the degree of burden experienced by caregivers of elderly patients with incontinence in a Greek community of the prefecture of Magnesia.

Methodology: During the period 02/2013-04/2014, we selected 300 caregivers, who were divided into three groups. Group I consisted of 100 caregivers of elderly patients with various diseases besides urinary incontinence, Group II of 100 caregivers of elderly patients who had urinary incontinence effectively treated with medication, and group III of 100 caregivers of elderly patients with severe untreated incontinence. The survey used the Zarit questionnaire.

Results: In groups I and II, about half of the sample experienced a "moderate to severe burden". In group III, the majority of caregivers experienced a severe burden (37%). The mean values of the total degree of burden differ significantly among the three groups ($p = 0.024$).

Conclusion: The study highlighted the need for psychosocial and financial support for caregivers of patients with incontinence, to reduce the burden they experience.

Key words
ageing; urinary incontinence; caregivers; burden; Zarit questionnaire

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Corresponding author:
Athanasios Zachariou, MD, Ph.D, FEBU, Elpis Hospital, Urology Department
3 Spyridi Street, Volos 38221, Tel: 00302421026937, Fax: 00302421026932, E - mail: zahariou@otenet.gr

Introduction

Population ageing is directly associated with the increased occurrence of diseases related to old age, such as Alzheimer's dementia, urinary incontinence etc. This creates increased health and social care needs, which are more difficult to serve due to the simultaneous reduction in the number of younger people who could care for dependent elderly.

Urinary incontinence is a common condition in men and women of all ages[1,2]. The prevalence of the disease ranges from 10 to 30% in the general population, while, in the elderly, it reaches 70%[3]. Urinary incontinence not only aggravates the quality of life of elderly patients living in the community, but is also an important element that affects the mental health and quality of life of their caregivers.

Providing care for the elderly is a process that entails an extensive physical, mental, emotional, financial and social burden for caregivers[4,5,6,7]. The assessment of the multiple effects of this burden is very important, as there are differences in gender, social status, psychological characteristics and intensity of care. As the effects of assuming the role of caregiver on physical and mental health are very important and as caregivers constitute an invaluable yet hidden social asset, research regarding the prevention of the burden on caregivers became a top priority for researchers of many disciplines, as well as for policy-makers in the field of health in many countries[8,9].

Elderly people with incontinence require time-consuming care and, depending to the severity of the condition and the coexistence of other diseases, often require changes in family structure[10,11]. The issue of family caregivers has not been extensively discussed in Greece, because in the past there was a widespread belief that families have not only an obligation but also the capacity to provide traditional informal care to their elderly members. Caring for these people is not only a valuable contribution to the family's finances but extends to the entire society and the state. However, the uninterrupted provision of care is an extremely exhausting process, which leads to increased psychiatric morbidity (depression), a loss of self of the caregiver, social isolation and the limitation of their personal relationships[12]. Finally, the high levels of burden observed among caregivers soon make them ineffective in their work, expediting the transfer of their patients to long-term care institutions, with socially and financially detrimental effects[13].

The international experience on the subject of this paper is limited. There are some notable studies, most of which concern the last decade[14,4,15,16,17,18,6,19,20]. These studies highlight the issue of incontinence as a significant element of burden for caregivers, especially when combined with other old-age conditions, such as dementia. They show that as the needs of patients increase because of incontinence, so do the demands for their care. This leads to a further burden for caregivers and increases the probability of confining the elderly in care homes.

The purpose of this study is to assess the burden on the mental health and quality of life of caregivers of elderly patients with urinary incontinence, living in the prefecture of Magnesia. This is a qualitative, cross-sectional, analytical study, which shows the current situation for the population of caregivers during the period in which it was conducted.

Methodology

Study population

The study lasted from February 2013 to April 2014. We selected 300 caregivers and their patients from the records of a private general clinic with a neurological department and a private recovery and rehabilitation centre. Elderly people constituted a convenience sample, meaning that access to their homes and communication were easy. The survey was conducted in urban and rural areas of the prefecture of Magnesia.

The control population (group I) comprised one hundred caregivers of elderly patients with various conditions (strokes, Parkinson's disease, post-operative recovery after major surgery, dementia, etc.) who did not present urinary incontinence. Group II comprised one hundred caregivers of elderly patients who presented urinary incontinence, in addition to the above conditions. In this group, given that they were treated with anticholinergics (solifenacin, oxybutynin, tolterodine), the elderly presented limited urine leakage (drops) or only an urgent need to urinate, which did not necessitate the use of aids such as diapers. An urgent need to urinate is the feeling that it is difficult to put off urination, which requires instantly finding a toilet to avoid the loss of urine. Finally, group III evaluated the caregivers of another one hundred elderly patients with severe incontinence that could not be treated or where there was no intention for its treatment, in which case the

TABLE 1	*The questions for each factor of the Burden Scale*		
FACTOR 1	**FACTOR 2**	**FACTOR 3**	**FACTOR 4**
Personal intensity	**Intensity of role**	**Deprivation of relationships**	**Management of care**
Questions	***Questions***	***Questions***	***Questions***
8. Do you feel that your relative is dependent on you?	1. Do you feel that your relative asks for more help than he/she needs?	2. Do you believe that, because you spend a lot of time with your relative, you do not have enough time for yourself?	20. Do you feel that you should be doing more for your relative?
9. Do you feel stress when you are with your relative?	4. Do you feel embarrassed by your relative's behaviour?	3. Do you feel pressure to choose between the care you provide to your relative and your efforts to meet other responsibilities regarding your family or work?	21. Do you feel that you could manage the care of your relative better?
10. Do you feel that your health suffers because of your involvement with your relative?	5. Do you feel angry when you are with your relative?	11. Do you feel that you do not have as much of a personal life as you would like because of your relative?	
14. Do you feel that your relative seems to expect you to care for him/her as if you were the only person on which he/she could rely?	6. Do you feel that your relative currently affects your relationships with other family members or with friends negatively?	12. Do you feel that your social life suffers because you are caring for your relative?	
15. Do you feel that, in addition to your regular expenses, you do not have enough money to take care of your relative?	7. Are you afraid of what the future holds for your relative?		
16. Do you feel that you are unable to continue caring for your relative?	13. Do you feel uncomfortable having your friends around because of your relative?		
17. Do you feel that you have lost control of your personal life since your relative fell ill?	19. Do you feel uncertain about what you should be doing for your relative?		
18. Do you simply wish that you could just leave the care of your relative to someone else?			
22. In general, how often do you feel burdened by caring for your relative?			

use of diapers or even external catheters was necessary.

The study conducted appropriate sampling with a non-random convenience sample[21]. Specifically, the first group filled in 65 questionnaires from urban areas (Volos, Almyros, Nea Anchialos) and 35 questionnaires from rural areas of the prefecture of Magnesia, the second group 69 questionnaires from urban areas and 31 from rural areas and the third group 51 and 49 questionnaires respectively. In group I, we initially approached 137 caregivers by telephone to inform them and obtain a preliminary oral consent for their inclusion in the study, in group II 149 and in group III 140. The caregivers' rates of reluctance to participate were similar in all three groups.

Research tools

Our basic research tool was the Zarit Burden Scale (BS) (Zarit Burden Interview, ZBI), which was first published in 1984 in the US[22]. It is a brief, valid and reliable method for assessing the burden experienced by those caring for a family member suffering from dementia. It is widely used in American and European countries to assess the burden experienced by caregivers of elderly patients suffering from conditions other than dementia, for which it was initially proposed.

In this study, we used the BS because it has been translated into Greek, the tool has been psychometrically tested and its validity has been verified. The translation and adaptation may change the internal structure, and thus the reliability and validity of the revised tool should be ensured. We requested and received permission to use the Greek version of the BS from the scholars who translated and certified the Zarit questionnaire in Greek.

The BS consists of 22 questions and was designed to assess the feelings of people who care for elderly people with dementia (**Table 1**). The rating is as follows: 0= never, 1= rarely, 2= sometimes, 3= fairly often and 4=

TABLE 2	*Demographic characteristics of caregivers (number and percentage)*		
	GROUP I	GROUP II	GROUP III
Sex			
Male	24	17	15
Female	76	83	85
Age			
29-40	10	12	9
41-51	29	27	28
51-61	29	34	40
62-88	32	27	23
Marital status			
Single	20	18	15
Married	69	73	77
Divorced	11	9	8
Educational level			
Basic studies	27	31	35
Secondary education	53	54	57
Tertiary education	20	15	8
Occupation			
Home-maker, unemployed	32	35	39
Dim. Employee	19	15	11
Pr. Employee	17	16	14
Freelancer	10	9	8
Retired	22	25	28
Relationship to patient			
Spouse	26	25	21
Child	49	45	45
Brother/Sister	2	1	1
Other	23	29	33
Accommodation			
In the same house	55	61	73
In a nearby house	31	17	7
In the same city	14	22	20
Information about incontinence			
None	-	37	45
Limited knowledge	-	47	51
Extensive knowledge	-	16	4
Months of care			
6-12	19	17	16
13-24	40	42	42
25-36	13	14	15
37-48	10	9	8
48-120	18	18	19

TABLE 3 *Distribution of the individual scales and the overall burden scale in group I*

	Mean Value (standard deviation)	Median (25th -75th percentile)
Personal Intensity (0-36)	20.28 (7.8)	20.51 (13.7-27.7)
Intensity of role (0-28)	12.84 (5.6)	13.23 (8.8-17.4)
Deprivation of relationships (0-16)	9.74 (4.0)	9.91 (6.8-13.2)
Management of care (0-8)	3.89 (1.7)	4.06 (2.2-5.4)
Total burden scale (0-88)	46.75 (16.1)	47.48 (31.5-60.4)

TABLE 4 *Distribution of the individual scales and the overall burden scale in group II*

	Mean Value (standard deviation)	Median (25th -75th percentile)
Personal Intensity (0-36)	21.26 (7.6)	21.52 (14.9-28.9)
Intensity of role (0-28)	13.87 (5.2)	14.14 (9.6-18.5)
Deprivation of relationships (0-16)	10.24 (3.7)	10.57 (7.6-13.7)
Management of care (0-8)	4.12 (1.5)	4.43 (2.8-5.7)
Total burden scale (0-88)	49.49 (17.1)	50.89 (34.2-63.1)

almost always (5-point Likert scale). Higher scores are indicative of a greater burden on the caregiver, with a maximum of 88.

According to Papastavrou et al. 2006[22], the factor analysis of the 22 questions of the BS (with the Principal Components method with Varimax rotation), provided 4 factors (which correspond to four sub-scales of caregiver burden).

For the statistical analysis, we used the SPSS statistical package (Statistical Package for Social Sciences v. 16.0, Chicago, Illinois, USA).

Results

All individuals participating in the study (n=300) were divided into three (3) groups consisting of 100 caregivers each. We selected to include 100 caregivers in each group because each subgroup resulting from the analysis of the results automatically equates to % percentages of the original group. **Table 2** shows the demographic characteristics of the sample of 100 caregivers in each study group.

The majority of caregivers were women (76% - 85%) with a mean age of 53 (groups I and II) and 55 years (group III). The mean age of men was 52 years (group I) and 53 years (groups II and III). The age difference between sexes was not statistically significant (p= 0.067). The mean age of the sample was 53.1 years (standard deviation 9.1 years). The majority of caregivers in the sample were married (69%, 73% and 77% respectively in the three groups).

In all groups, the percentage of home-makers, unemployed and pensioners was above 50%, which shows that care requires several hours of work. Most caregivers were children of the patients. In the third group, the co-

TABLE 5	*Distribution of the individual scales and the overall burden scale in group III*	
	Mean Value (standard deviation)	Median (25th -75th percentile)
Personal Intensity (0-36)	23.2 (8.1)	23.72 (15.8-30.1)
Intensity of role (0-28)	15.61 (5.5)	15.94 (10.3-20.8)
Deprivation of relationships (0-16)	11.03 (3.9)	11.37 (7.6-14.2)
Management of care (0-8)	4.44 (1.6)	4.71 (3.2-6.0)
Total burden scale (0-88)	54.28 (16.1)	55.29 (40.2-68.1)

habitation percentages with the elderly show a statistically significant difference (p= 0.078), which underlines the severity of these cases. The mean length of patient care was 38 months (standard deviation 19.8 months) with a median of 3.1 years of care. As regards the length of care, no statistically significant difference is observed among the three groups.

As regards education, the results show that, in group III, less educated people are employed as caregivers, as those with more skills can choose better posts. This is in line with the level of knowledge caregivers have about urinary incontinence. The paradox is that those dealing with the most severe cases have the least information about managing the problem and the possible available solutions. The reported sources of information included watching medical programs on TV, the presence of relatives or friends with similar problems and magazines.

Table 3 shows the distribution of the individual scales and of the overall caregiver burden scale for group I, **Table 4** for group II and **Table 5** for group III. The mean and median ranged around the middle of the relevant scale, indicating an average burden. In group I, the mean total burden score was 46.75 (standard deviation 16.1) and 75th percentile with a value of 60.4, with a maximum of 88. The reliability of the burden scale was excellent (Cronbach's alpha= 0.91).

The mean and median for caregiver group II ranged around the middle of the relevant scale, indicating an average burden (Table 3). The mean total burden score was 49.49 (standard deviation 17.1) and 75th percentile with a value of 63.1, with a maximum of 88. The reliability of the burden scale was excellent (Cronbach's alpha= 0.87).

In group III, the mean total burden score was 54.28 (standard deviation 16.1) and 75th percentile with a value of 68.1, with a maximum of 88 (Table 4). It is clear that the third group shows the highest burden rates in relation to the other two groups. The reliability of the burden scale was excellent (Cronbach's alpha= 0.84).

In group I, there is no study on the knowledge of caregivers about incontinence, as this group includes caregivers who take care of elderly with general health problems but without incontinence. Their knowledge on the subject does not affect the level of burden. Women caregivers aged over 50, the married, unemployed, pensioners, caregivers with a low level of education and those living in the same house with the elderly patient present a greater burden. The only statistically significant difference concerns the length of care (p= 0.032), where those who have acted as caregivers for over 2 years have a greater burden.

In group II, the findings are similar to those for group I. The only difference is observed in the occupation of the caregiver and on information about incontinence. Caregivers who are employed have significantly lower burden rates than those who do not work or are home-makers (p= 0.065) in percentages that tend to be statistically significant. Finally, caregivers who have knowledge on the therapeutic approach to incontinence present low burden rates as they are better able to manage the problems of the elderly (p= 0.053).

In **Table 6**, amongst the caregivers in group III, caregivers who are employed show statistically significant lower burden rates than those who do not work or are home-makers (p= 0.034). Caregivers with tertiary edu-

TABLE 6 *Comparison of the role burden scale depending on the characteristics of the sample of caregivers in group III*

Total Burden Scale (scale range 0-88)			
	Mean value (standard deviation)	Median (25th-75th per.)	*p*-value
Sex			0.202
Male	50.3 (14.4)	52.9 (38.8 - 60.8)	
Female	55.8 (15.1)	57.4 (40.8 - 68.7)	
Age			0.346
<= 50	52.4 (15.0)	55.9 (38.6 - 63.7)	
> 50	56.3 (15.5)	58.5 (41.7 - 69.8)	
Marital status			0.206
Married	57.9 (15.7)	58.6 (39.8 - 67.7)	
Single/Divorced	53.2 (15.3)	55.1 (43.8 -67.2)	
Educational level			0.049
Basic studies	58.5 (15.2)	59.4 (39.4 - 68.5)	
Tertiary education	50.3 (15.8)	49.9 (35.1 - 62.6)	
Occupation			0.034
Home-maker, unemployed, retired	58.8 (15.1)	60.5 (42.2 - 70.1)	
Employee	51.5 (15.2)	52.1 (36.7 - 64.1)	
Relationship to patient			0.654
Child	53.9 (15.5)	54.5 (38.8 - 65.7)	
Other	53.8 (15.8)	54.9 (38.7 - 66.7)	
Accommodation			0.248
In the same house	53.6 (15.6)	54.2 (38.7 - 67.4)	
In a nearby house / same city	53.9 (15.4)	55.8 (38.4 - 65.0)	
Information about incontinence			0.043
Limited/None	58.9 (15.7)	59.1 (39.9 - 68.3)	
Abundant	51.3 (15.6)	51.9 (35.9 - 63.4)	
Months of care			0.030
<= 24	50.4 (15.7)	52.1 (34.9 - 62.9)	
> 24	61.0 (15.4)	63.0 (45.0 - 74.4)	

cation better manage the burden of care in a statistically significant percentage (p= 0.049) compared to those with basic education. Of course, it should be emphasised that almost all caregivers in this category are nurses, graduates of Technological Educational Institutes or nursing assistants. Finally, good knowledge on managing the problems associated with incontinence (care of the external catheter, appearance of blood in the urine collector etc.) leads to statistically significant lower caregiver burden (p= 0.043).

It is characteristic that the caregivers who have jobs and present the lowest burden are unmarried or divorced men, who state that they do not reside in the same house with the elderly patient. Especially in group III, with the greatest burden, the caregivers of elderly patients with incontinence or a catheter, caregivers who are employed stay in their own home (78%) are male (89%), unmarried or divorced (81%). On the contrary, non-employed caregivers live in their own homes at a rate of 29% are women (91%) and married (64%). Of

course, it should be noted that length of care should be considered as the most important burden factor, as in the case of elderly patients with incontinence, 11% of caregivers stay in their own home and are women at a rate of 97%.

Discussion

In this study, most caregivers in all three groups were women (76 - 85%). This finding is consistent with other studies in Greece on demented patients[23,24,25] and on the elderly in general[26,27]. Study group III shows higher rates of women caregivers in relation to those for demented patients, which is justified by the greater care and cleanliness that a patient with incontinence requires. This high proportion of women is explained by the belief of old that a daughter or a daughter-in-law has an obligation to look after the elderly relative who "wets himself", in combination with the inability of women to easily find work, especially in the current economic conditions. Even when care is provided by a paid helper, then again this is usually a woman. The mean age of women caregivers in this category (53-55 years) in fact means that women are excluded from the labour market and cannot receive a pension under the new law. These caregivers have not alternatives in the labour market. Women form the majority of caregivers in almost all surveys on the subject conducted abroad[20,16,6].

As regards living with the elderly patient, groups I and II present rates similar to those for patients with dementia (57 - 60%)[23,24] or the elderly[26]. In group III, this percentage jumps to 73% and it is clear that the elderly with incontinence require constant cleaning. This makes it necessary for caregivers to be by the patient all day long. It is characteristic that, if they do not stay in the same house, Greeks caregivers who are children of the elderly patients live in the same building or within walking distance.

Furthermore, the results of this study show that the percentage of caregivers in groups I and II belonging to the burden group with a score of 41-60 in the ZBI scale are similar (48% and 45% respectively), while in group III this percentage drops. This score, corresponding to "moderate to severe burden" is consistent with findings from other studies on dementia patients[23,24,13]. Group III presents a significant increase in the percentage of caregivers who experience a "severe burden", which corresponds to a score of 61 - 88 in the Zarit scale. Thus, while the rates are 25% in group I and 28% in group II, in group III this reaches 37%, which in practice means that 1 in 3 caregivers of incontinent elderly patients experiences a severe burden. The high rates of group III indicate the synergistic effect of incontinence with other factors creating a burden for caregivers. The findings for group III are in line with the findings of the study by Tamanini et al.[20] in the city of Sao Paulo in Brazil, where the burden on caregivers of elderly patients with incontinence was 1.96 times higher than the burden on those of non-incontinent elderly. In a similar work by Cassels & Watt[16], conducted in Australia, the heavy burden on the spouses of elderly people with incontinence led the authors to the conclusion that where a holistic approach to the problem is not possible, the pharmaceutical management of incontinence alone suffices to alleviate the burden of care.

The other social and demographic characteristics that present a positive correlation with increased burden are the length of care and the lack of work. 32% of caregivers who provide services to elderly people for over >24 months in group II and 45% in group III present a severe burden.

A high correlation is also observed between the variables of the place of residence and work of caregivers. Specifically, in group I, 61% of caregivers who live in the same house with the patient stated that they do not work or are retired. The corresponding percentage in group III reaches 85%, indicating that the hours spent caring for the elderly patient do not allow a different occupation. On the contrary, in group I, of those who live in a different house from the patient, 64% are employed. This percentage falls in group III 24% and concerns younger caregivers and especially all the men in this category. A similar study by Gotoh et al.[6] conducted *via* the internet in Japan, in a sample of 1,324 caregivers of elderly incontinent patients, emphasised that the caregiver's cohabitation with the elderly patient leads to high rates of burden.

Another important finding is the impact of the caregivers' tertiary education and their knowledge on managing incontinence on the burden of care. These two elements are probably interrelated. The better and higher the caregivers' education level, the better they are able to gain information on the incontinence of the elderly patient and to assess likely difficult situations. The feeling of helplessness described by caregivers with ba-

sic education and the intense need for information described in the interviews greatly increases their burden. Finally, let us not forget that the category of caregivers with knowledge and tertiary education is paid more than others with a lower education level.

It should be mentioned that caregivers with tertiary education are better placed to access the appropriate services for informing the relatives of the elderly patient about the incontinence aids that can be covered by their insurance fund. Most of these conducted searches on the internet and facilitated several elderly patients financially. Therefore, the caregivers' education level is an important factor in providing quality care to incontinent patients. The necessity of the education of caregivers of elderly incontinent patients is also raised as an imperative issue in other works studied[20,16,6].

A major limitation of the study is the non-random sampling method used. A deliberate and non-random convenience sample allows the easy identification and use of all available populations for the study. The results of data processing may be representative of the sample isolated but probably not of the broader set of caregivers of elderly incontinent patients in Volos. The last drawback is, in part, offset by the large number of elderly patients in the study (total 300) and by the existence of a control group. Moreover, the validity and reliability of the filled-in scales can be contested when they are based on the self-assessment of caregivers about their experiences and cannot be verified objectively. Thus, the scoring reflects the personal perception of caregivers about their burden, rather than the degree of difficulty caused by the patient. The researcher cannot be absolutely sure about the honesty of responses on sensitive issues such as the issue of care.

This study provides an overview of the current situation as regards the care of people with urinary incontinence in a provincial town and the burden experienced by caregivers. The study results showed that caring for a patient with incontinence is associated with an increased burden. It also showed that there are multiple factors that could predict the burden, which means that this problem should be approached in a broad clinical and social context. The main conclusion is the recognition of the need for further exploring the concept of burden and the impact of care on the physical and psychiatric morbidity of the people who care for patients with incontinence.

Conflict of interest

The authors declared no conflicts of interest.

Περίληψη

Σκοπός: Η πληθυσμιακή γήρανση συνδέεται άμεσα με την εμφάνιση ασθενειών που συνδέονται με την τρίτη ηλικία, όπως η ακράτεια ούρων. Αυτή δεν επιβαρύνει μόνο την ποιότητα ζωής των ηλικιωμένων ασθενών, αλλά ταυτόχρονα αποτελεί σημαντικό στοιχείο που επιδρά στην ψυχική υγεία και την ποιότητα ζωής των φροντιστών των ασθενών αυτών. Σκοπός της μελέτης είναι η εκτίμηση του βαθμού επιβάρυνσης που βιώνουν οι φροντιστές ηλικιωμένων ασθενών με ακράτεια σε μία ελληνική κοινότητα του νομού Μαγνησίας.

Μεθοδολογία: Κατά το χρονικό διάστημα 02/2013 - 04/2014 επιλέχθηκαν 300 φροντιστές οι οποίοι χωρίσθηκαν σε τρεις ομάδες. Η ομάδα Ι περιελάμβανε 100 φροντιστές ηλικιωμένων με διάφορες παθήσεις εκτός ακράτειας ούρων, η ομάδα ΙΙ 100 φροντιστές ηλικιωμένων που παρουσίαζαν ακράτεια ούρων η οποία αντιμετωπιζόταν αποτελεσματικά με φαρμακευτική θεραπεία, και στην ομάδα ΙΙΙ φροντιστές 100 ηλικιωμένων με σοβαρού βαθμού ακράτεια που δεν αντιμετωπιζόταν. Στην έρευνα χρησιμοποιήθηκε το ερωτηματολόγιο Zarit.

Αποτελέσματα: Στις ομάδες Ι και ΙΙ περίπου οι μισοί βίωσαν «μέτρια έως σοβαρή επιβάρυνση». Στην ομάδα ΙΙΙ το μεγαλύτερο ποσοστό των φροντιστών παρουσίασε υψηλού βαθμού επιβάρυνση (37%). Οι μέσες τιμές ως προς το συνολικό βαθμό επιβάρυνσης στις τρεις ομάδες διαφέρουν στατιστικά σημαντικά μεταξύ τους (p= 0,024).

Συμπέρασμα: Η μελέτη ανέδειξε την ανάγκη ψυχοκοινωνικής και οικονομικής στήριξης των φροντιστών ασθενών με ακράτεια, ώστε να μειωθεί η επιβάρυνση που υφίστανται.

Λέξεις ευρετηριασμού

γήρανση, ακράτεια ούρων, φροντιστές, επιβάρυνση, ερωτηματολόγιο Zarit

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CASE REPORT

Renal tract tuberculosis in a young man with chronic flank pain and lower urinary tract symptoms

David Thurtle[1], Victor Manolas[1], Helen Burgess[2], Konstantinos Charitopoulos[1]
[1]Department of Urology, West Middlesex University Hospitals NHS Trust, Twickenham Road, London, TW7 6AF
[2]Department of General Medicine, West Middlesex University Hospitals NHS Trust, Twickenham Road, London, TW7 6AF

Abstract

We present here a case of a 37-year old white male, of African origin, who presented on numerous occasions with lower urinary tract symptoms and flank pain. He eventually was admitted with acute on chronic renal failure.
Inpatient investigations demonstrated bilateral ureteric obstruction secondary to stricture disease. A nephrostomy was placed to the functioning right kidney but antegrade ureteric stenting was impossible. Rigid cystoscopy demonstrated a low-capacity bladder with copious debris. Early morning urine samples, eventually demonstrated mycobacterium, alongside bladder biopsy samples which demonstrated caseous granulomas. The patient was treated, under nephrology and TB physicians with quadruple anti-TB therapy with considerable improvements in his renal function.
This case was noteworthy because: the patient had never had pulmonary TB, we were successfully able to demonstrate positive urine cultures and the outcome was positive. We compare this case to the available literature and reflect upon the delays in diagnosis and potential improvements to management.

Key words
tuberculosis; obstructive uropathy; renal tract tuberculosis; ureteric stricture disease

Citation
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Introduction

Lower urinary tract symptoms (LUTS) such as poor flow, urinary frequency and nocturia are very common complaints in urology outpatient departments. Flank pain, or 'renal colic' is a common presentation to Emergency departments. However, the prevalence of these presenting complaints does not guarantee the ultimate diagnosis is straight - forward.

Corresponding author:
David Thurtle, E - mail: davidthurtle@gmail.com

We present a case of a 37 - year old male with a 4 year history of progressively worsening LUTS and left flank pain. Amongst other factors, the diagnosis was delayed by failing to keep a broad differential diagnosis or thinking beyond the common causes.

This case also serves as a reminder that the prevalence of tuberculosis is increasing in Europe. The effects of renal tract TB can be widespread and severe. Given its insidious onset and that a history of primary, pulmonary TB may not be noted, the diagnosis can be delayed or missed. This case was not only interesting and unusual, but also a useful reflective exercise about our own practice

Case Presentation

Mr C initially presented to the urology outpatient department in 2010, aged 33. He was a Portuguese - speaking white gentleman, born in Mozambique who had moved to the UK, via Portugal, in 2008. He worked as a chef at a nearby airport. He had never smoked, does not drink alcohol and eats a balanced diet. His wife and 3 children still live in Mozambique. He reported a past medical history of only 'an enlarged prostate', he had never been hospitalised before, nor had he ever knowingly had tuberculosis or any chest complaint.

Mr C had been referred by his GP with hesitancy, poor flow, and urinary frequency; passing urine 10 times per day and 4 times at night. Following this initial consultation a flexible cystoscopy was planned but the patient never attended and was lost to follow - up. Over a year later he presented to the emergency department, on two separate occasions, with left flank pain. He reported these two episodes were typical of flank pain he regularly experienced and for which he took ibuprofen regularly. On both occasions he had a CTKUB but was not admitted. A clinic appointment was arranged in February 2012 as a result of the CT findings(discussed later). From clinic, urine cultures and serology for schistosomiasis were sent and a follow - up ultrasound and flexible cystoscopy arranged but again the patient did not attend. Finally, in November 2013 Mr C was again re - referred to urology clinic with worsening LUTS although he still felt systemically well. Blood results on the day demonstrated a creatinine of 716μmol/L and urea of 30.8mmol/L, he was admitted for further investigations as an inpatient.

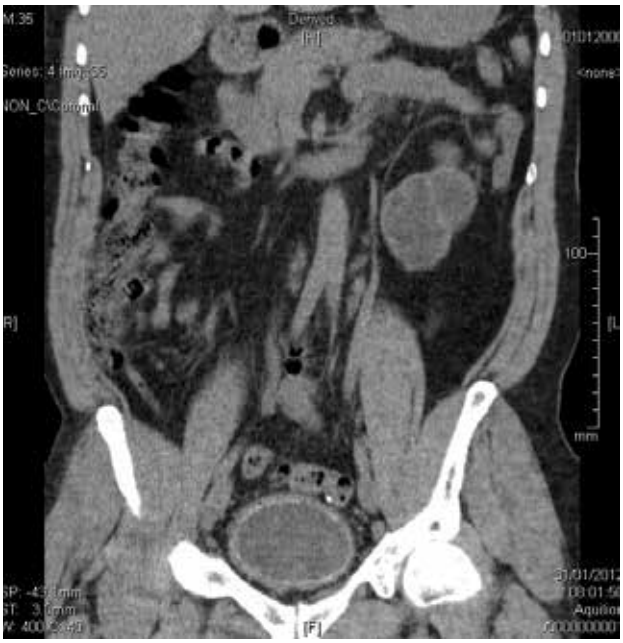

Figure 1: *Coronal non - contrast CT from 1 year prior to hospital admission. Performed by the emergency department for renal colic. The left kidney has an unusual appearance with thin cortex and large central hypodense area and lobulated margin. In addition there is nonspecific increased density or calcification of the bladder wall*

Investigations

The two CTKUBs in 2012 had demonstrated left sided Pelvi - calyceal dilatation, without a dilated ureter and marked thinning of the left renal cortex. On the right, the kidney cortex appeared normal but a dilated pelvi - calyceal system and ureter were noted. The second scan also noted possible circumferential calcification of the bladder wall **(Figure 1)**. A follow - up USSKUB confirmed the findings but demonstrated an apparently normal Doppler blood flow in both renal parenchyma.

Urinalysis in the emergency department had demonstrated microscopic haematuria and in clinic had demonstrated leucocytes, without nitrites, but routine urine cultures had grown no pathogens.

A flexible cystoscopy, performed on the day of admission demonstrated a stricture in the penile urethra 2cm from the urethral orifice which the cystoscope was unable to pass. Urine flow testing demonstrated very poor stream (Qmax 4.9ml/s, average 2.7ml/s).

An ultrasound during admission showed an enlarged, 14cm right kidney with pelvicalyceal dilatation and a 4.8 cm 'cystic area' with 'sloughing of the pyramids'. The left kidney was again noted to have very thin cortex and appear cystic.

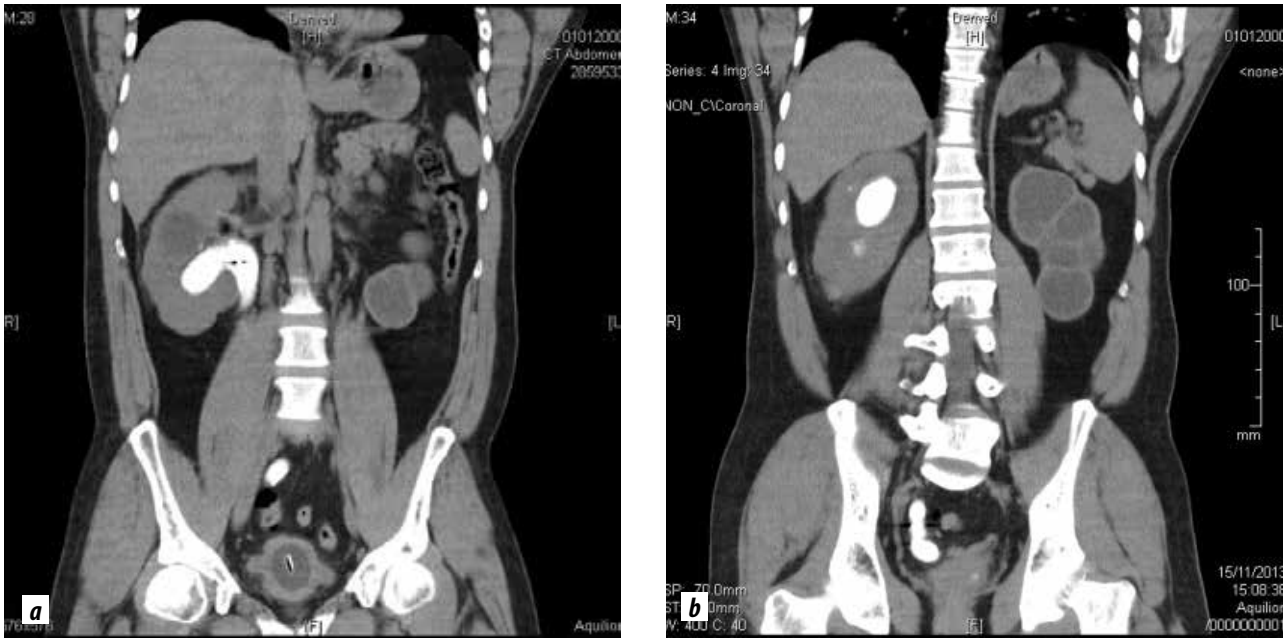

Figure 2: a. *Coronal CT sections performed after nephrostomy and attempted retrograde stent insertion. Note the dilated renal pelvis of the right kidney.* ***b.*** *Note how the distal ureter is swollen yet no contrast is able to pass to the empty bladder - demonstrating severe stricture disease*

Treatment

On presentation, the urethra was dilated and a urethral catheter placed, the residual volume was only 65ml. Later, a right nephrostomy was inserted to protect the hydronephrotic right kidney. Fluid optimisation and IV hydration was performed with Mr C entering a post - obstructive diuresis phase, producing up to 8,000ml/day. An antegrade stent could not be passed during this procedure, with obstruction noted at the right vesico - ureteric junction. CT images with contrast were obtained following the procedure, demonstrating dilated renal pelvis and right ureter, but no passage of contrast through to the urinary bladder **(Figure 2a, Figure 2b)**. Once the nephrostomy was in place, there was zero urine output via the urethral catheter confirming a non - functioning left renal unit.

Retrograde attempts to identify and stent the right ureteric orifice were unsuccessful with the bladder wall noted to be inflamed with copious debris in the bladder. Subsequent histology of bladder biopsies demonstrated caseous granuloma.

During admission, creatinine values fell, before plateauing at 400µmol/L. Multiple investigations during a prolonged inpatient stay included a positive TB Elispot test and 3 separate early - morning urines (EMU). After 9 days incubation one of these EMU grew fully - sensitive Mycobacterium tuberculosis.

Mr C was commenced on quadruple TB therapy (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide) for 8 weeks then reduced to triple therapy (Rifampicin, Isoniazid and Ethambutol) to complete 1 year. High - dose prednisolone was commenced to aid renal function, alongside appropriate bone and stomach protection.

Outcome and follow - up

6 months after discharge Mr C remains well and compliant with his medication. He copes well with a right - sided nephrostomy and has returned to work. His visual acuity had deteriorated such that ethambutol was stopped, his vision has subsequently recovered. His creatinine count has fallen to 274µmol/L and CRP normalised.

A recent nephrostogram failed to demonstrate any passage of contrast in to the urinary bladder suggesting stenting may still be impossible. Unfortunately, his attendance to appointments is not reliable, we hope to perform further urodynamics assessment of his bladder prior to definitive reconstruction of the urinary tract.

Discussion

Tuberculosis (TB) remains a large global healthcare

problem. The incidence of disseminated and extra - pulmonary disease is rising[1]. After peripheral lymphadenopathy, genito - urinary TB is the most common form of extra - pulmonary TB. 8 - 15% of patients with pulmonary TB develop infection in the genito - urinary system[2]. Mycobacteria bacilli reach distant organs by haematogenous spread, TB of the urinary tract then takes a descending route of infection[3]. Genito - urinary effects of TB can be broad and varied including renal calcification, necrosis, stricture disease throughout the urothelium and bladder contractures[3 4]. Renal failure can, therefore, be caused by damage to the renal parenchyma itself, or by obstructive uropathy.

In this case stricture disease was evident in the penile urethra, right vesico - ureteric junction and can be assumed to have been present in the left renal unit causing complete non - functionality. Mr C was hospitalised before his kidney function was irreversibly damaged. Although no such cases have been found in recent Western medical literature, two similar cases have been published in Brazilian journals, with less successful outcomes. One reports a 33 - year old man with 3 years intermittent history of flank pain presenting in renal failure, despite best care he remains on lifelong haemodialysis[5]. The second reports a 32 - year old female with recent history of peritoneal TB who, despite 6 months anti - tuberculosis therapy, presented in acute renal failure secondary to TB which was ultimately fatal[6]. Unlike our case - in both of these cases a clear history of pulmonary TB was elicited and indeed these presented in areas where TB is endemic. Also satisfying within our case is that we were able to demonstrate positive mycobacterium urine cultures. A Moroccan review of 109 urogenital TB cases found bacilli in only 41 (38%) of their patients,[7] indeed these two aforementioned published reports were unable to demonstrate positive urine cultures.

On retrospective analysis of this case we considered clues that may have led to earlier diagnosis. Initial urinalysis had demonstrated sterile pyuria and microscopic haematuria, a common finding in urinary tract TB along with acidic urine[8]. Irritative lower urinary tract symptoms, which fail to improve with routine antibiotics should raise the possibility of TB[9].

Radiological investigations can also demonstrate signs suggestive of TB. USS, CT and IVU can all be helpfully used, with CTIVU the most sensitive at identifying all manifestations of renal tuberculosis[10]. Signs progress from papillary necrosis in early disease to multifocal strictures and mural thickening prior to endstage progressive hydronephrosis, parenchymal thinning and dystrophic calcification. Even the non - contrast CTs performed on Mr C in 2012, showing abnormal left kidney size, should perhaps have been reviewed in a multi - disciplinary meeting. This case serves as a reminder of the importance of strong communication within and between departments, and coordinated strategies to reliably follow - up patients; all the more important as modern healthcare becomes more sub - specialised.

Conflicts of interest

The authors declared no conflicts of interest.

Περίληψη

Παρουσιάζουμε την περίπτωση ενός 37 χρόνου άνδρα, Αφρικανικής καταγωγής, που παρουσιάστηκε στα εξωτερικά ιατρεία με συμπτώματα του κατώτερου ουροποιητικού και οσφυικό πόνο. Η εισαγωγή του έγινε με κλινική εικόνα οξείας σε έδαφος χρόνιας νεφρικής ανεπάρκειας. Κατά την παραμονή του στην Κλινική οι διάφορες εξετάσεις ανέδειξαν αμφοτερόπλευρη απόφραξη των ουρητήρων και τοποθετήθηκε νεφροστομία στον πιο λειτουργικό δεξιό νεφρό καθώς η τοποθέτηση JJ stent δεν ήταν δυνατή. Η άκαμπτη κυστεοσκόπηση ανέδειξε ουροδόχο κύστη περιορισμένης χωρητικότητας ενώ στα δείγματα πρωινών ούρων και στην παθολογοανατομική εξέταση βιοψίας της κύστης απεδείχθη φυματίωση του ουροποιητικού. Ο ασθενής έλαβε τετραπλή αντι-φυματική αγωγή και υπήρξε σημαντική βελτίωση της νεφρικής του λειτουργίας. Η περίπτωση αυτή είναι ενδιαφέρουσα καθώς ο συγκεκριμένος ασθενής δεν είχε ποτέ νοσήσει με πνευμονική νόσο ενώ ταυτόχρονα θελήσαμε να αναδείξουμε την πάθηση ώστε να βελτιωθεί ο τρόπος με τον οποίο αντιμετωπίζονται παρόμοια περιστατικά.

Λέξεις ευρετηριασμού

φυματίωση ουροποιητικού, αποφρακτική ουροπάθεια, στένωση ουρητήρων

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CASE REPORT

A forgotten intravesical foreign body. A not so unusual story

Spyridon Tzamarias, George Makris, Dimitrios Zavradinos, George Panaretos, Konstantinos Stamatiou
Urology department, Tzaneio General Hospital, Pireas

Abstract

We report the case of a 67 - year - old woman who presented with recurrent lower urinary tract symptoms due to bladder calculus that formed around a ureteral stent that was inserted into her drainage system during stone removal surgery from the renal pelvis 6 years previously. In this paper we present the evaluation, imaging and management of the above case. Our patient's case was unique for the length of time (6 yr) from foreign body insertion to presentation.

Key words
bladder calculi; ureteral stent; foreign body

Citation
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Introduction

Foreign bodies in the urinary bladder are common and they have always been an interesting topic. Actually many urologists occasionally reported a great variety of foreign bodies removed from the lower urinary tract of female and male patients. The majority of them are self inserted and few are iatrogenically induced. Among others needles, electrical wires, segments of wooden sticks, safety pins, thermometers, bullets, animal feather, intrauterine contraceptive devices, encrusted sutures, piece of candles, lead pencil, surgical staples with stones, pieces of gauzes, chewing gum, tooth brush, metallic hook, tip of ureteric catheter, broken stent and parts of endoscopic instruments have been reported in the literature[1,2]. In most of the cases, patients are presented because of the complications of the presence of foreign bodies in the urinary tract. In fact, the foreign body if not removed leads to bacterial colonization and so acts as a nidus for recurrent infections. Rarely may also cause pelvic pain, hematuria, retention and secondary stones. Hereby, we report the case of a 67 - year - old woman who presented with recurrent urinary infections due to bladder calculi that formed around a ureteral stend that was inserted into her drainage system during a stone removal surgery from the renal pelvis 6 years previously.

Case report

A 67 - year - old woman presented to the emergency department with lower urinary tract symptoms. She

Corresponding author:
Dr. Stamatiou Konstantinos, 2 Salepoula str., 18536 Piraeus, Greece, Tel:+302104592311, E - mail: stamatiouk@gmail.com

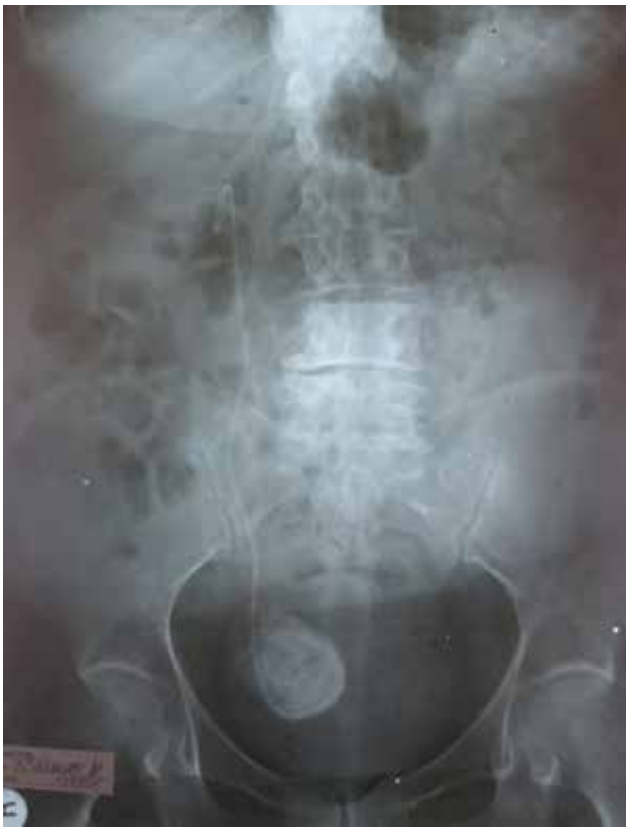

Figure 1: *Plain x-ray reveales a large bladder calculus and a double Z ureteral stent in the right ureter*

Figure 2: *Bladder calculus and stent after removal*

reported irritative symptoms for more than two years. More precisely, she reported sporadic episodes of inflammatory pain and increased urgency of urination while she had a constant increased frequency of urination the last six years. Her symptoms progressed over a period of 15 days to include fever and suprapubic pain. Her medical history included mild hypertension, and diabetes mellitus which were not actively treated. She had no history of urinary tract infections, sexually transmitted infections or urinary tract calculi. She also reported a stone removal surgery from the right renal pelvis 6 years previously. Initial investigations revealed mild leukocytosis (10.2×10^9/L), mild elevated creatinine levels (1.4 μmol/L) and positive urinalysis for red blood cells, protein and nitrites. Blood and urine cultures were negative. Ultrasound of the abdomen and pelvis revealed mild right hydroureteronephrosis and mild renal cortical thinning. The urinary bladder showed detrusor hypertrophy and contained a large calcificated mass. Plain x - ray of the abdomen revealed a large bladder calculus and the presence of a double J ureteral stent in the right ureter **(Figure 1)**. At the time of admission, she denied having ureteral stent. However, investigation of her medical file confirmed a ureteral stent placement into her right drainage system during stone removal surgery. She was started on broad - spectrum antibiotics and underwent cystoscopy, which showed a large, freely mobile bladder calculus. We removed the calculus and the forgotten stent by subsequent open cystolithotomy. Notably the stent was severely calcified and encrusted only at its lower edge and no crystal deposit or stone formation was seen at median part and the upper end of stent **(Figure 2)**. We closed the bladder in 2 layers, leaving an indwelling urethral catheter and a perivesical drain. The patient had an uncomplicated postoperative recovery.

Discussion

Risk factors for bladder calculi include urinary stasis, infection and the presence of foreign bodies. Typical presentations include bladder outlet obstruction, urinary tract infection, terminal hematuria, intermittent pain and irritating urinary symptoms such as frequency, urgency and dysuria. Foreign bodies are mainly in-

troduced into the bladder by self - insertion, which is usually a result of eroticism, by penetrating injuries or iatrogenically, via migration from adjacent organs. In a few cases medical devices remain forgotten in situ. The forgotten ureteral stents remain a urological dilemma and complications related to it can be lethal for the patient[3]. There are several cases reported in the literature the main causes of which were poor patient compliance with instructions to return for stent removal, and inadequate counsel by practitioners[4]. The management of such stents is often intriguing[5]. Depending upon the size of the foreign body, either minimally invasive procedures such as lithotripsy, endoscopic management or open surgical exploration are recommended[6]. Our patient's case was unique for the absence of severe infection for 6 years and the absence of crystal deposit or stone formation was seen at median part and the upper end of stent. In fact encrustation of forgotten ureteral stents usually occurs at the upper coil of the stent[7]. Although the exact mechanism of encrustation is not clear, more effective peristalsis at the lower part of the stent sweeps any deposits off the stent, thus minimizing encrustation at the lower end[6]. However, Dakkak et al in an analysis of 22 patients with encrusted ureteral stent found that encrustation is more common in the bladder (68.2%) and ureter (59%) than in the kidney (36.4%). According to these authors this happens because, urine remains in the bladder for a longer time than in the upper urinary tract[8].

Conclusion

Foreign body - induced bladder calculi are a diagnostic and therapeutic challenge. The prevention of this problem by providing patient education is of outmost importance and therefore protective mechanisms should be designed.

Conflicts of interest

The authors declared no conflicts of interest.

Περίληψη

Αναφέρουμε την περίπτωση μίας 67χρονης γυναίκας με υποτροπιάζοντα ενοχλήματα από το κατώτερο ουροποιητικό που οφείλονταν σε λίθο της ουροδόχου κύστης που σχηματίστηκε γύρω από ένα ουρητηρικό καθετήρα που εισήχθη στο αποχετευτικό σύστημα του δεξιού νεφρού της κατά τη διάρκεια χειρουργικής επέμβασης αφαίρεσης λίθου από τη νεφρική πύελο πριν από 6 χρόνια. Σε αυτό το άρθρο παρουσιάζεται η αξιολόγηση, η απεικόνιση και η διαχείριση της παραπάνω περίπτωσης. Αυτή η περίπτωση είναι μοναδική για το χρονικό διάστημα (6 έτη) από την εισαγωγή στην του ξένου σώ-

Λέξεις ευρετηριασμού

λίθος της ουροδόχου κύστης, ουρητηρικός καθετήρας, ξένο σώμα

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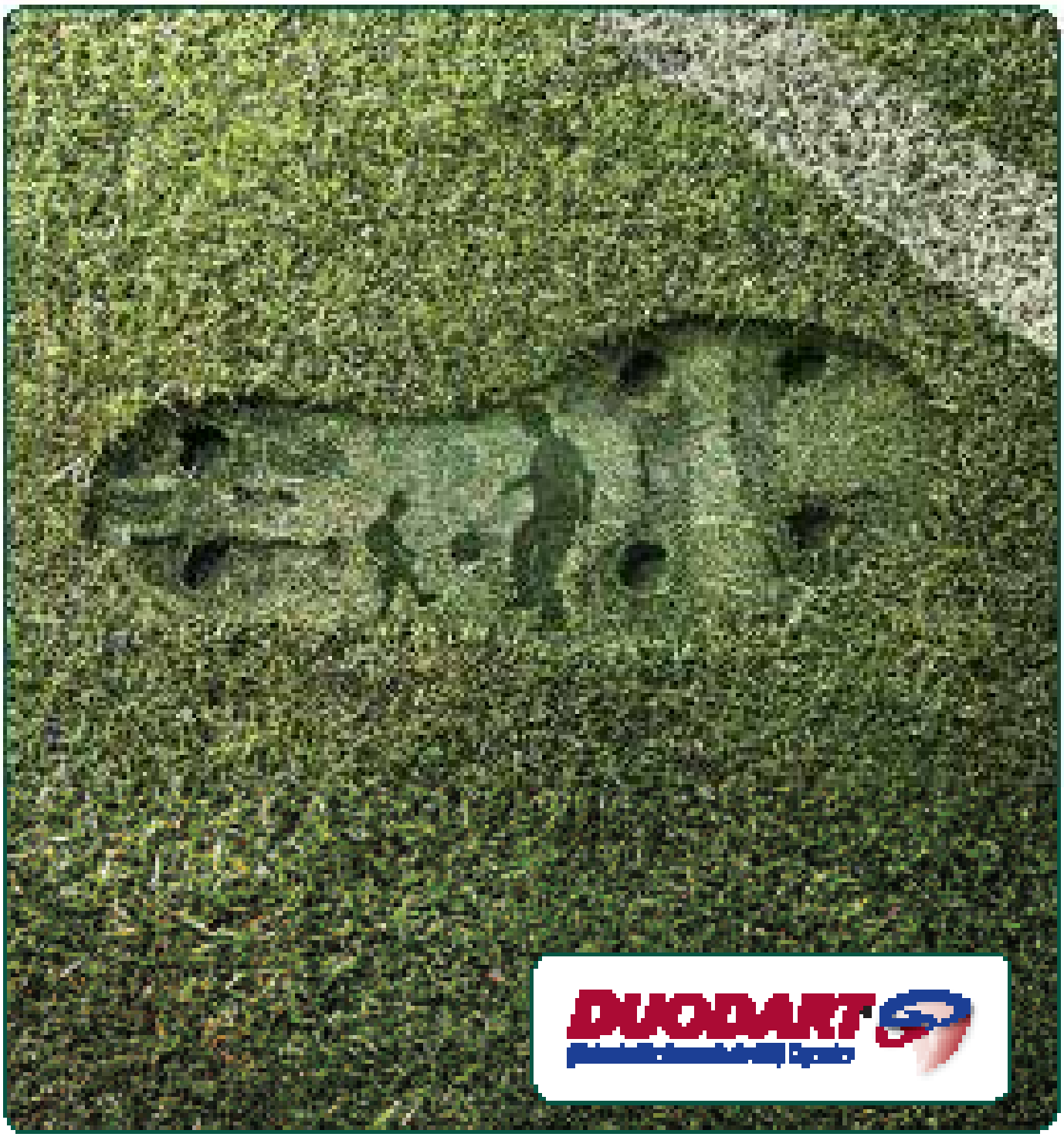
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ΠΕΡΙΛΗΨΗ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Arvekap 11,25 mg/vial (3 μηνών). **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** Ένα φιαλίδιο περιέχει 15mg triptorelin pamoate, που αντιστοιχεί σε 11,25mg triptorelin. Για τον πλήρη κατάλογο των εκδόχων βλέπε παράγραφο 6.1. **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ:** Κόνις και διαλύτης για ενέσιμο εναιώρημα. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1. Θεραπευτικές Ενδείξεις: - Καρκίνος του προστάτη:** Θεραπεία του τοπικά προχωρημένου ή μεταστατικού καρκίνου του προστάτη (ευνοϊκή επίδραση της θεραπείας είναι εμφανέστερη και συχνότερη σε ασθενείς που δεν είχαν λάβει προηγουμένως άλλη ορμονική θεραπεία). **- Ενδομητρίωση:** Γεννητική και εξωγεννητική ενδομητρίωση (στάδιο I-IV). **- Ινομυώματα μήτρας:** Θεραπεία των ινομυωμάτων μήτρας. **- Πρώιμη ήβη:** Προ της ηλικίας των 8 ετών στα κορίτσια και των 10 ετών στα αγόρια. **4.2. Δοσολογία και τρόπος χορήγησης: - Καρκίνος του προστάτη:** Μία ενδομυϊκή ένεση του Arvekap 11,25mg κάθε τρεις μήνες. **- Ενδομητρίωση:** Μία ενδομυϊκή ένεση του Arvekap 11,25mg κάθε τρεις μήνες. Η θεραπεία πρέπει να αρχίζει τις πρώτες πέντε ημέρες του καταμήνιου κύκλου. Διάρκεια της θεραπείας ενδομητρίωσης: αυτή εξαρτάται από την αρχική βαρύτητα της ενδομητρίωσης και τις αλλαγές που παρατηρούνται στην κλινική εικόνα (λειτουργικές και ανατομικές) κατά τη διάρκεια της θεραπείας. Γενικά, συνιστάται η ενδομητρίωση να θεραπεύεται για διάστημα 3 μηνών και μόνον αν αποδειχθεί στους 3 μήνες ότι η θεραπεία απέδωσε μπορεί να συνεχισθεί το ανώτερο μέχρι 6 μήνες. Δεν πρέπει να χορηγείται δεύτερη σειρά θεραπείας με αυτό το φαρμακευτικό προϊόν ή άλλο ανάλογο γοναδορελίνης. **- Ινομυώματα:** Μία ενδομυϊκή ένεση του Arvekap 11,25mg κάθε τρεις μήνες. Η θεραπεία πρέπει να αρχίζει τις πρώτες πέντε ημέρες του καταμήνιου κύκλου. Γενικά, συνιστάται τα ινομυώματα να θεραπεύονται για διάστημα 3 μηνών και μόνον αν αποδειχθεί στους 3 μήνες ότι η θεραπεία απέδωσε μπορεί να συνεχισθεί το ανώτερο μέχρι 6 μήνες. **- Πρώιμη ήβη:** Παιδιά βάρους άνω των 20 kg λαμβάνουν μία ενδομυϊκή ένεση του Arvekap 11,25mg κάθε τρεις μήνες. Η θεραπεία θα πρέπει να διακοπεί όταν πιθανόν η φυσιολογική ηλικία της ήβης και δεν θα πρέπει να συνεχίζεται σε κορίτσια με οστική ηλικία μεγαλύτερη των 12 ετών. Υπάρχουν περιορισμένα διαθέσιμα δεδομένα σε αγόρια σχετικά με τον άριστο χρόνο διακοπής της αγωγής βάσει της οστικής ηλικίας, ωστόσο προτείνεται η διακοπή της αγωγής σε αγόρια με οστική ηλικία 13-14 ετών. Για λεπτομερείς οδηγίες στη μέθοδο χορήγησης, βλέπε παράγραφο 6.6 "Οδηγίες χρήσης / χειρισμού". **4.3. Αντενδείξεις:** - Υπερευαισθησία στη γοναδορελίνη, τα ανάλογά της ή σε οποιοδήποτε άλλο συστατικό του φαρμάκου (βλέπε παράγραφο 4.8 "Ανεπιθύμητες ενέργειες"). - Σε ασθενείς με καρκίνο του προστάτη που παρουσιάζουν συμπίεση του νωτιαίου μυελού ή ενδείξεις μετάστασης. - Κύηση. Πριν την έναρξη της αγωγής πρέπει να επιβεβαιώνεται ότι η ασθενής δεν είναι έγκυος. **4.4. Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Σε ενήλικες, η παρατεταμένη χρήση αναλόγων GnRH μπορεί να οδηγήσει στην απώλεια οστικής μάζας γεγονός που αυξάνει τον κίνδυνο οστεοπόρωσης. Ρύθμιση της αντιυπερτασικής θεραπείας μπορεί να απαιτείται σε ασθενείς οι οποίοι λαμβάνουν τέτοια αγωγή. **- *Καρκίνος του προστάτη:*** Η τριπτορελίνη, όπως και τα άλλα ανάλογα GnRH, προκαλεί αρχικά μια παροδική αύξηση στα επίπεδα ορού της τεστοστερόνης, και πιθανά επακόλουθη επιδείνωση των συμπτωμάτων που σχετίζονται γενικά με τον καρκίνο του προστάτη. Για να αντιρροπιστεί αυτή η αρχική αύξηση των επιπέδων τεστοστερόνης, μπορεί να εξεταστεί η χορήγηση αντιανδρογόνων κατά την έναρξη της θεραπείας. Ασθενείς που παρουσιάζουν ή έχουν αυξημένο κίνδυνο για ανάπτυξη απόφραξης των ουροφόρων οδών ή συμπίεσης του νωτιαίου μυελού πρέπει να παρακολουθούνται στενά. Είναι χρήσιμος ο περιοδικός έλεγχος των επιπέδων τεστοστερόνης αίματος, καθώς αυτά δεν πρέπει να ξεπερνούν το 1 ng/ml. **- *Ενδομητρίωση - Ινομυώματα:*** Η χορήγηση τριπτορελίνης στη συνιστώμενη δοσολογία προκαλεί συνεχή υπογοναδοτροφική αμηνόρροια. Εάν συμβεί μητροραγία μετά από τον πρώτο μήνα, πρέπει να μετρηθούν τα επίπεδα της οιστραδιόλης στο πλάσμα και εάν αυτά τα επίπεδα είναι κάτω από 50 pg/ml, πρέπει να αναζητηθούν πιθανές οργανικές βλάβες. Η ωοθηκική λειτουργία επανέρχεται μετά από τη διακοπή της θεραπείας και η ωορρηξία συμβαίνει περίπου 5 μήνες μετά την τελευταία ένεση. Μία μη ορμονική μέθοδος αντισύλληψης θα πρέπει να χρησιμοποιείται σε όλη τη διάρκεια της αγωγής περιλαμβανομένων και 3 μηνών μετά την τελευταία ένεση. **- *Πρώιμη ήβη:*** Η αρχική διέγερση των ωοθηκών στα κορίτσια, μπορεί να προκαλέσει αιμορραγία από τη μήτρα. Επιβάλλεται η τουλάχιστον ετήσια παρακολούθηση των ασθενών μέχρι τη διακοπή της θεραπείας. **4.5. Αλληλεπιδράσεις με άλλα φάρμακα και άλλες μορφές αλληλεπίδρασης:** Να μη χορηγείται ταυτόχρονα με φάρμακα που προκαλούν υπερπρολακτιναιμία (μειώνουν τον αριθμό των υποδοχέων της GnRH στην υπόφυση). Δεν έχει παρατηρηθεί άλλη κλινικά σημαντική αλληλεπίδραση με άλλα φαρμακευτικά προϊόντα. **4.6. Κύηση και Γαλουχία: - *Κύηση:*** Μελέτες σε πειραματόζωα δεν έδειξαν τερατογόνο επίδραση. Κατά τη διάρκεια της επιτήρησης μετά την κυκλοφορία στην αγορά και σε περιορισμένο αριθμό εγκύων γυναικών με έκθεση στην τριπτορελίνη, δεν υπήρξαν αναφορές γενετικών ανωμαλιών ή εμβρυοτοξικότητας οι οποίες να αποδίδονται στο προϊόν. Εντούτοις, επειδή ο αριθμός των ασθενών είναι πολύ μικρός για την εξαγωγή συμπερασμάτων όσον αφορά στον κίνδυνο συγγενών ανωμαλιών ή εμβρυοτοξικότητας, εάν η ασθενής καταστεί έγκυος ενώ λαμβάνει τριπτορελίνη, η θεραπεία πρέπει να διακοπεί. Μία μη ορμονική μέθοδος αντισύλληψης θα πρέπει να χρησιμοποιείται σε όλη τη διάρκεια της αγωγής περιλαμβανομένου και 1 μηνός μετά την τελευταία ένεση. **- *Γαλουχία:*** Η τριπτορελίνη δεν συνιστάται να χρησιμοποιείται κατά την περίοδο του θηλασμού. **4.7. Επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανών:** Δεν έχουν παρατηρηθεί επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανών. **4.8. Ανεπιθύμητες ενέργειες:** ***Εμπειρία από τις κλινικές μελέτες*:** Τα στοιχεία που αναφέρονται κατωτέρω βασίζονται στην ανάλυση των αθροιστικών δεδομένων που αναφέρθηκαν κατά τη διάρκεια κλινικών μελετών με την μηνιαία και την τρίμηνη μορφή του φαρμάκου (συνολικός πληθυσμός περίπου 2400). Η πλειοψηφία των ανεπιθύμητων ενεργειών που αναφέρθηκαν κατά τη διάρκεια των κλινικών μελετών σχετίζονταν με τις φαρμακολογικές δράσεις, όπως ο υπογοναδοτροφικός υπογοναδισμός, ή η αρχική διέγερση της υπόφυσης και των γονάδων. Η συχνότητα των ανεπιθύμητων ενεργειών που αναφέρονται παρακάτω, ορίζεται με βάση την ακόλουθη αρχή: Πολύ συχνές (≥ 10%) – Συχνές (≥ 1% - <10%) - Μη συχνές (≥0,1 - <1%) - Σπάνιες (≥0,01 - <0,1%) – Πολύ σπάνιες (<0,01%). Γενική ανοχή σε ενήλικες: Πολύ συχνές: Ήπιες μέχρι έντονες εξάψεις και εφιδρώσεις οι οποίες συνήθως δεν απαιτούν διακοπή της θεραπείας. Γενική ανοχή σε άνδρες: Πολύ συχνές κατά την έναρξη της θεραπείας (βλ. παράγραφο 4.4 "Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση"): Επιδείνωση συμπτωμάτων εκ του ουροποιητικού, οστικός πόνος μεταστατικής αιτιολογίας και συμπτώματα που σχετίζονται με συμπίεση του νωτιαίου μυελού από σπονδυλικές μεταστάσεις (πόνος οσφύος, αδυναμία, παραισθησία των κάτω άκρων), όταν τα επίπεδα τεστοστερόνης πλάσματος αυξάνονται αρχικά και παροδικά κατά την έναρξη της αγωγής. Αυτά τα συμπτώματα είναι παροδικά και συνήθως εξαφανίζονται σε μία έως δύο εβδομάδες. Συχνές κατά τη διάρκεια της θεραπείας: Ελαττωμένη σεξουαλική επιθυμία και ανικανότητα στύσης που σχετίζονται με τη μείωση των επιπέδων πλάσματος τεστοστερόνης πλήγω της φαρμακολογικής δράσης της τριπτορελίνης. Γενική ανοχή σε γυναίκες: Πολύ συχνές κατά την έναρξη της θεραπείας: - Επιδείνωση συμπτωμάτων ενδομητρίωσης (πυελικός πόνος, δυσμηνόρροια) κατά τη διάρκεια της αρχικής και παροδικής αύξησης των επιπέδων οιστραδιόλης πλάσματος. Αυτά τα συμπτώματα είναι παροδικά και συνήθως εξαφανίζονται σε μία έως δύο εβδομάδες. -Αιμορραγία εκ του γεννητικού συστήματος περιλαμβάνοντας μηνορραγία, μητρορραγία, μπορεί να συμβεί κατά τον μήνα που ακολουθεί την πρώτη ένεση. Πολύ συχνές κατά τη διάρκεια της αγωγής: Κατά τη διάρκεια των κλινικών μελετών στην ενδομητρίωση οι ανεπιθύμητες ενέργειες έδειξαν μια γενική μορφή υποοιστρογονικών συμπτωμάτων που σχετίζονταν με την καταστολή της υπόφυσης και των ωοθηκών, όπως διαταραχές ύπνου, κεφαλαλγία, διαταραχές θυμικού, κολπική ξηρότητα, δυσπαρεύνια και μειωμένη σεξουαλική επιθυμία. Πολύ συχνές κατά τη διάρκεια της αγωγής με την μηνιαία μορφή του φαρμάκου: πόνος στήθους, μυϊκές κράμπες, αρθραλγία, αύξηση βάρους, ναυτία, κοιλιακός πόνος / δυσφορία, εξασθένηση. Γενική ανοχή σε παιδιά: Αντιδράσεις υπερευαισθησίας, κεφαλαλγία, εξάψεις, και αιμορραγία εκ του γεννητικού συστήματος στα κορίτσια (βλ. παράγραφο 4.4 "Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση"). Τοπική ανοχή: Συχνές: πόνος, ερυθρότητα και φλεγμονή στο σημείο της ένεσης. ***Εμπειρία μετά την κυκλοφορία του προϊόντος:*** Σε ενήλικες: Κατά τη διάρκεια της επιτήρησης μετά την κυκλοφορία του προϊόντος έχουν αναφερθεί επιπλέον πολύ σπάνιες ανεπιθύμητες ενέργειες. Αυτές ταξινομούνται κατά κατηγορία οργάνων σώματος και κατά μειούμενη συχνότητα εμφάνισης. - Ενδοκρινικές διαταραχές: γυναικομαστία. - Ψυχιατρικές διαταραχές: κατάθλιψη, αλλαγή της προσωπικότητας. - Διαταραχές νευρικού συστήματος: ζάλη, παραισθησία σε άντρες. - Οφθαλμικές διαταραχές: θολή όραση ή διαταραχές της όρασης. - Διαταραχές ώτων και λαβυρίνθου: ίλιγγος που μερικές φορές σχετίζεται με γαστρεντερικά συμπτώματα. - Διαταραχές αναπνευστικές, θώρακος και μεσοθωρακίου: δύσπνοια. - Γαστρεντερικές διαταραχές: διάρροια, έμετος. - Διαταραχές δέρματος και υποδόριου ιστού: αντιδράσεις υπερευαισθησίας που περιλαμβάνουν κνησμό, κνίδωση, εξάνθημα, αγγειοοίδημα (βλ. παράγραφο 4.3 "Αντενδείξεις"). - Διαταραχές μυοσκελετικές, οστικές και συνδετικού ιστού: αρθραλγία, μυαλγία και μυϊκή αδυναμία σε άνδρες και γυναίκες, επεισόδια οστικού πόνου σε άνδρες κατά τη διάρκεια της αγωγής (βλ. επίσης παράγραφο 4.4 "Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση", σχετικά με τον κίνδυνο οστεοπόρωσης). - Διαταραχές του αναπαραγωγικού συστήματος και μαστού: σε γυναίκες, παρατεταμένες διαταραχές περιόδου όπως αμηνόρροια, μηνορραγία και μητρορραγία μετά την αγωγή. Βλ. σχετικά με την ενδομητρίωση και τα ινομυώματα μήτρας στην παράγραφο 4.4 "Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση". - Γενικές διαταραχές και καταστάσεις σημείου χορήγησης: πυρεξία, κακουχία. - Εξετάσεις: αυξημένη αρτηριακή πίεση. Σε παιδιά: Σύμφωνα με την συσωρευμένη εμπειρία ασφάλειας της τριπτορελίνης σε παιδιά που έλαβαν αγωγή για την πρώιμη ήβη, οι ακόλουθες σπάνιες ανεπιθύμητες ενέργειες έχουν αναφερθεί επιπλέον κατά την επιτήρηση μετά την κυκλοφορία του προϊόντος: αντιδράσεις υπερευαισθησίας, κεφαλαλγία, αύξηση βάρους, αυξημένη αρτηριακή πίεση, επεισόδια θολής ή διαταραγμένης όρασης, δυσφορία εκ του γαστρεντερικού με κοιλιακό πόνο και εμετό, επίσταξη, κακουχία, μυαλγία, συναισθηματική αστάθεια, νευρικότητα. **4.9. Υπερδοσολογία:** Δεν έχουν αναφερθεί ανεπιθύμητες αντιδράσεις οφειλόμενες σε υπερδοσολογία. Σε περίπτωση υπερδοσολογίας, ενδείκνυται συμπτωματική αντιμετώπιση. **5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ: 5.1. Φαρμακοδυναμικές ιδιότητες:** *ΑΝΑΛΟΓΟ ΤΗΣ ΕΚΛΥΤΙΚΗΣ ΟΡΜΟΝΗΣ ΤΩΝ ΓΟΝΑΔΟΤΡΟΦΙΝΩΝ.* ***Κωδικός ATC****: L02AE04 (αντινεοπλαστικό και ανοσοτροποποιητικό).* Η τριπτορελίνη είναι συνθετικό δεκαπεπτίδιο που είναι ανάλογο της φυσικής εκλυτικής ορμόνης των γοναδοτροφινών (γοναδορελίνη, GnRH, LH-RH). Μελέτες σε ζώα και στον άνθρωπο έχουν δείξει ότι η συνεχής χορήγηση τριπτορελίνης, μετά από μία αρχική διέγερση, αναστέλλει την έκκριση των γοναδοτροφινών με επακόλουθη καταστολή της λειτουργίας των όρχεων και της ωοθήκης. Η πρώτη ένεση του Arvekap 11,25 mg διεγείρει την απελευθέρωση των υποφυσιακών γοναδοτρόφων LH και FSH προκαλώντας μία παροδική αύξηση των επιπέδων τεστοστερόνης στους άνδρες και οιστραδιόλης στις γυναίκες (flare-up). Η παρατεταμένη χορήγηση οδηγεί, περίπου 20 ημέρες μετά και καθ' όλη τη διάρκεια απελευθέρωσης της δραστικής ουσίας, σε μείωση των επιπέδων LH και FSH και κατά συνέπεια σε πτώση της τεστοστερόνης ή οιστραδιόλης πλάσματος σε επίπεδα ευνουχισμού. Μια παροδική αύξηση των όξινων φωσφατασών μπορεί να παρτηρηθεί σε άνδρες κατά την έναρξη της θεραπείας. Στην πρώιμη ήβη η αναστολή της υποφυσιακής γοναδοτροφικής υπερδραστηριότητας και στα δύο φύλα, οδηγεί στην καταστολή της αιχμής της LH μετά από διεγερτική δοκιμασία LHRH και συνεπώς καταστολή της έκκρισης οιστραδιόλης ή τεστοστερόνης και σε βελτίωση του λόγου ηλικία ως προς το ύψος / οστική ηλικία και του τελικού ύψους. **5.2. Φαρμακοκινητικές ιδιότητες:** Μετά την ενδομυϊκή ένεση του Arvekap 11,25mg στους ασθενείς με καρκίνο του προστάτη, παρατηρείται μία μέγιστη τιμή της τριπτορελίνης πλάσματος περίπου 3 ώρες μετά την ένεση. Μετά από μία φάση ελάττωσης που συνεχίζεται κατά τη διάρκεια του πρώτου μήνα, τα επίπεδα τριπτορελίνης στην κυκλοφορία παραμένουν σταθερά μέχρι την ημέρα 90. Το επίπεδο τεστοστερόνης στο αίμα φθάνει στο όριο ευνουχισμού περίπου 20 ημέρες μετά την ένεση και παραμένει σημαντικά κάτω από αυτό το όριο καθ' όλη τη διάρκεια απελευθέρωσης της δραστικής ουσίας αντιστοιχώντας με τη φάση σταθεροποιημένης συγκέντρωσης στο πλάσμα. **5.3. Προκλινικά στοιχεία για την ασφάλεια:** Τα μόνα προκλινικά ευρήματα ήταν αυτά που σχετίζονταν με την αναμενόμενη φαρμακολογική δράση της τριπτορελίνης, δηλαδή την καταστολή του υποθαλαμο-υποφυσιακού –γοναδικού άξονα, με το επακόλουθο αποτέλεσμα στα επίπεδα των ορμονών του φύλου και στον αναπαραγωγικό άξονα. Αυτά τα ευρήματα ήταν σε μεγάλο βαθμό αναστρέψιμα κατά την περίοδο ανάκαμψης. Η τριπτορελίνη δεν έχει δειχθεί να είναι τοξική στο γενετικό υλικό στην κλασσική σειρά δοκιμασιών μεταλλαξογένεσης. Η εμφάνιση αδενωματωδών όγκων στην υπόφυση αρουραίων που παρατηρήθηκε με το Arvekap στα πλαίσια μακροχρόνιων μελετών καρκινογένεσης, είναι μία ειδική δράση των αναλόγων της γοναδορελίνης σε αυτό το είδος ζώων, που προκαλείται μέσω ενός ορμονικού μηχανισμού και δεν έχει παρατηρηθεί στον ποντικό ούτε έχει περιγραφεί στον άνθρωπο. Η απορρόφηση του Arvekap 11,25mg ολοκληρώνεται σε 120 ημέρες. **6. ΦΑΡΜΑΚΕΥΤΙΚΑ ΣΤΟΙΧΕΙΑ: 6.1. Κατάλογος με τα έκδοχα:** Κόνις: Polymere dl-lactide glycolide q.s.p., Mannitol, Carmellose sodium, Polysorbate 80, Nitrogen. Διαλύτης: Mannitol, Ύδωρ ενεσίμων. **6.2. Ασυμβατότητες:** Δεν αναφέρονται. **6.3. Διάρκεια ζωής:** 36 μήνες. **6.4. Ιδιαίτερες προφυλάξεις κατά την φύλαξη του προϊόντος:** Φύλαξη σε θερμοκρασία το ανώτερο μέχρι 25° C. Μετά την ανασύσταση να χρησιμοποιείται αμέσως. **6.5. Φύση και συστατικά του περιέκτη:** - Γυάλινο φιαλίδιο 4ml με ελαστομερές πώμα και κάλυμμα αλουμινίου, που περιέχει το στερεό λυόφιλο. - Γυάλινη φύσιγγα 2ml που περιέχει τον υγρό διαλύτη για ανασύσταση. - 1 αποστειρωμένη σύριγγα από πολυπροπυλένιο (3 ml). - 2 αποστειρωμένες βελόνες 0.9mm. **6.6. Οδηγίες χρήσης/χειρισμού:** Το στερεό λυόφιλο θα πρέπει να ανασυσταθεί με τον υγρό διαλύτη αμέσως πριν την ένεση. Δεν πρέπει να αναμειγνύεται με άλλα φάρμακα. 1 – ΠΡΟΕΤΟΙΜΑΣΙΑ ΑΣΘΕΝΟΥΣ: -Ο ασθενής ξαπλώνει και απολυμαίνεται η περιοχή του γλουτού όπου θα γίνει η ένεση. 2 – ΠΡΟΕΤΟΙΜΑΣΙΑ ΤΗΣ ΕΝΕΣΗΣ: -Η παρουσία φυσαλίδων στην επιφάνεια του στερεού λυόφιλου είναι φυσιολογική. -Σπάστε το πλαιό της φύσιγγας του διαλύτη. -Αναρροφήστε όλο τον διαλύτη στη σύριγγα με την βελόνα. -Αφαιρέστε το πράσινο κάλυμμα από το φιαλίδιο του στερεού λυόφιλου. -Μεταφέρετε τον διαλύτη από τη σύριγγα στο φιαλίδιο που περιέχει το στερεό λυόφιλο. -Τραβήξτε τη σύριγγα με τη βελόνα πάνω από την επιφάνεια του υγρού αλλά μην την αφαιρείτε τελείως από το φιαλίδιο. -Ανακινήστε το φιαλίδιο χωρίς να το αναστρέψετε έως ότου σχηματιστεί ένα ομοιογενές εναιώρημα. -Ελέγξτε για την απουσία συσσωματωμάτων πριν αναρροφήσετε το εναιώρημα (σε περίπτωση παρουσίας συσσωματωμάτων, συνεχίστε την ανακίνηση μέχρι να επιτευχθεί πλήρης ομογενοποίηση). -Αναρροφήστε με τη σύριγγα όλο το εναιώρημα χωρίς να αναστρέψετε το φιαλίδιο. -Αφαιρέστε από τη σύριγγα την βελόνα που χρησιμοποιήσατε για την ανασύσταση. Προσαρμόστε στη σύριγγα την άλλη βελόνα (βιδώστε σφιχτά) κρατώντας τη μόνο από το χρωματιστό τμήμα. -Αφαιρέστε τον αέρα από τη σύριγγα. 3 – ΕΝΕΣΗ: -Η ένεση πρέπει να γίνει χωρίς καθυστέρηση. Κάνετε την ένεση στον γλουτιαίο μυ. 4 – ΜΕΤΑ ΤΗ ΧΡΗΣΗ: -Απορρίψτε τις βελόνες σε κατάλληλο δοχείο. Κατά την διάρκεια των παραπάνω ενεργειών, κάθε απώλεια προϊόντος μεγαλύτερη από αυτή που φυσιολογικά παραμένει στο φιαλίδιο και τη σύριγγα, πρέπει να λαμβάνεται υπόψη από τον θεράποντα γιατρό. **6.7. Ονομασία και μόνιμη έδρα του Υπεύθυνου Κυκλοφορίας:** IPSEN ΕΠΕ, Αγ. Δημητρίου 63, Άλιμος 174 56, Αθήνα. **7. ΑΡΙΘΜΟΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** 78741/04-11-2009. **8. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΑΔΕΙΑΣ:** 13-6-2000. **9. ΗΜΕΡΟΜΗΝΙΑ ΤΗΣ (ΜΕΡΙΚΗΣ) ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ:** 4-11-2009.

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Η σύνδεση της «βιομηχανίας» Τουρισμού με την Υγεία γίνεται πραγματικότητα

Ιδρύθηκε και ξεκίνησε άμεσα την δραστηριότητα του ο Ελληνικός Σύνδεσμος Τουρισμού Υγείας.

Δημιουργήθηκε από επιφανή μέλη της τουριστικής βιομηχανίας και έγκριτους επιστήμονες υγείας, οι οποίοι διέγνωσαν τα σημαντικά πλεονεκτήματα και την προστιθέμενη αξία που μπορεί να έχει ο Τουρισμός Υγείας, στον Ελληνικό Τουρισμό, στον κλάδο της Υγείας και επιπρόσθετα στην Οικονομία και το ΑΕΠ της χώρας.

Σκοπός του Συνδέσμου είναι η σύνδεση, ανάπτυξη και διεύρυνση της «βιομηχανίας» του τουρισμού, με το πολύτιμο αγαθό της υγείας, μέσα από την συνεχή υποστήριξη και προβολή των παρακάτω κατηγοριών:

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ΔΥΟ FORUM 2017

Ο Ελληνικός Σύνδεσμος Τουρισμού Υγείας συμμετέχει στο ΔΥΟ Forum 2017

Με περίπτερο, στο οποίο θα ενημερώνει για τις πολλαπλές του δραστηριότητες, τους επαγγελματίες τουρισμού και υγείας, αλλά και με την διοργάνωση του τρίτου και μεγαλύτερου διεθνούς συνεδρίου για τον Ιατρικό Τουρισμό, συμμετέχει ο Σύνδεσμος, στο **ΔΥΟ Forum 2017**, που θα πραγματοποιηθεί στις **11 και 12 Φεβρουαρίου 2017, στο Ζάππειο Μέγαρο**.

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ΤΟ ΔΙΟΙΚΗΤΙΚΟ ΣΥΜΒΟΥΛΙΟ ΑΠΑΡΤΙΖΕΤΑΙ ΑΠΟ ΤΟΥΣ:

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Αντιπρόεδρος	Κουσκούκης Κωνσταντίνος, Καθηγητής Δερματολογίας - Νομικός, Πρόεδρος Ελληνικής Ακαδημίας Ιαματικής Ιατρικής
Γεν. Γραμματέας	Καπλανίδης Ζαχαρίας, Πρόεδρος Ομίλου Zita, Οικονομολόγος
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