The Multimodal Treatment of a Patient with Metastatic Prostate Cancer and the Highest PSA Reported in Romania

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ABSTRACT

Introduction and Objectives. Prostate cancer is the 2nd most common cancer in men worldwide. Latest prostate cancer data also shows that this pathology is the 4th most common cancer overall. There were more than 1.4 million new cases of prostate cancer in 2020. Guadeloupe had the highest incidence for prostate cancer in 2020, with 722 new cases, 183.6/100000 inhabitants. In Europe, Ireland, Estonia, Sweden and France are the countries with the highest incidence rate for prostate cancer.

Materials and Methods. We present the case of a 65 years old patient, which was diagnosed in July 2020 with a high risk prostate cancer. Firstly, he was referred to a Urology Clinic for a clinical examination and possibly to have a diagnosis formulated after an elevated prostate specific antigen (PSA) was observed in another medical setting. After a more precise measurement, the PSA was surprisingly high, a finding that was the trigger for a multidisciplinary approach, using the latest information and treatments described in important clinical trials.

Results. The evolution of the patient during the 32 months long surveillance period varied, as the PSA level fell and rose, prompting many changes in the treatment of the prostate cancer. Various clinical trials were reviewed in order to present the rationale for treatment changes occurring at certain moments.

Conclusions. Even though the metastatic high risk prostate cancer proves to be very difficult to treat, and the patients are still suffering from this pathology, the progress made in the last decade seem to improve the chances for a longer survival and a better quality of life.

Key-words: androgen deprivation therapy, chemotherapy, prostate cancer, prostate specific antigen, metastatic prostate cancer.

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INTRODUCTION AND OBJECTIVES

Prostate cancer is the 2nd most common cancer in men worldwide. Latest prostate cancer data also shows that this pathology is the 4th most common cancer overall. There were more than 1.4 million new cases of prostate cancer in 2020.

Two overseas departments of France are the regions with the most significant incidence in the world. Guadeloupe had the highest rate of prostate cancer in 2020, followed by Martinique, with 722 new cases, 183.6/100000 inhabitants, and 659 new cases, 168.2/100000 inhabitants, respectively. In Europe, Ireland, Estonia, Sweden and France are the countries with the highest incidence rate for prostate cancer. The numbers are $110.7/10^5$, $102.2/10^5$, $100.4/10^5$, $99/10^5$, respectively.[1]

According to Globocan, in Romania, prostate cancer was ranked 3rd in the overall population, after lung and breast cancers, with 8555 new cases reported in 2020. The incidence was 41.5 cases per 100000 individuals. The mortality was 10.7/100000, behind lung, breast and colorectal cancers, and very close to cervix uteri cancer (9.8/100000).[2]

We know that prostate cancer is an age related affliction and in the context of an ageing population, especially in Europe, this may prove a future inconvenience, not only for the individuals, but also for governments and healthcare organizations.[3] So, in this context we can foresee that Urology will be a medical specialty in very high demand.

MATERIALS AND METHODS

A patient, who is now 65, was referred to "Prof. Dr. Th. Burghele Hospital almost three years ago with the suspicion that he is suffering from an undiagnosed prostate cancer. He was complaining of shortness of breath during low intensity effort, back pains and lower urinary tract symptoms, and was known to have high blood pressure, congestive heart failure NYHA class III, coronary stenting in 1994, a percutaneous transluminal coronary angioplasty (PTCA), and an anteroseptal myocardial infarction in 2011 which required another stenting. During his first visit at the Hospital in July 2020, after a history check and brief a clinical examination, a PSA (prostate specific antigen) testing was performed, but given the fact that the laboratory has a PSA cutoff of 150 ng/mL the result showed a value of > 150 ng/mL, meaning that the actual value of the PSA can be of the order of hundreds or even thousands. So, the next step was to ask the patient for permission to do a digital rectal examination. During the local examination the prostate was assessed: a small volume gland, with increased consistency, especially hard in the apex of the right lobe. The patient was then referred to another laboratory for another PSA testing. After waiting for 6 days he had another PSA test. The result was a very hard to believe 11502 ng/mL. This was the incentive to swiftly hospitalize the patient for 24 hours and perform a prostate biopsy. In the meanwhile, he had a CT (computed tomography) scan, for the thorax, abdomen and pelvis, enhanced with contrast agent. The obvious metastatic burden (bone and lymphatic metastases) prompted the imagist to ask for a hematology consultation, because she suspected a myeloma.


synevo

Buletin de rezultate

Contract: CABINET MEDICAL MARIANA

chimie

11502 ng/mL

Fig. 1. Quantitative PSA test performed at a RENAR accredited laboratory which shows an incresed value 11502 ng/mL (Patient's personal archive)

On the 27.07.2020, while he was admitted in the hospital, a 6 core biopsy was performed using a transrectal ultrasound probe for guidance. First of all, an abdominal ultrasound was performed, in order to document the case. The abdominal ultrasound showed a small prostate (21 cubic centimeters), a hypoechoic nodule in the right lobe which was compressing the urethra. The biopsy procedure was performed under local anesthesia and was very well tolerated by the patient. He was able to leave the hospital in the evening of the same day.



Fig. 2. and 3. Ultrasound of the bladder and prostate showing a hyperechoic lesion at the base of the prostate and a hypoechoic lesion in the right lobe (From the patient's personal archive)

A bone scintigraphy was recommended, even before the results of the biopsy, because it seemed obvious that the patient was suffering from a metastatic prostate cancer, with bone metastases which were affecting the bone marrow. The locations for this metastasis were the skull cap, most of the bones of the rib cage, and the right femoral shaft. This bone metastases were the cause of the anemia from which the patient was suffering. During the first examination at "Prof. Dr. Th. Burghele" Hospital the hemoglobin was 8,6 g/dL, but was somewhat tolerated, the patient being able to slowly climb a few flights of stairs.

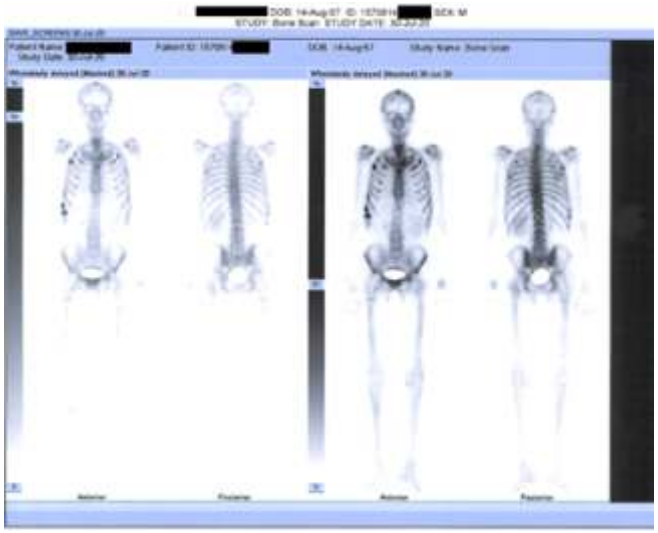


Fig. 4. Bone scintigraphy – numerous bone metastasis (rib cage, skull cap, femoral shaft - from the patient's personal archive)

The pathology report for the prostate biopsy was released on the 19th of August 2020. The pathologist described the 6 cores collected, summing 55 mm of prostatic tissue, 29 mm (53% of the total length) presenting malignant transformation with poorly differentiated cells. The Gleason Score was 5+4 for all the cores, three of them taken from the right prostatic lobe and three of them from the left lobe. There was also perineural invasion (PNI+) and lymphovascular invasion (LVI+). In the sixth core, taken from the left lobe, the pathologist was able to recognize adipocytes, meaning there was evidence for extracapsular extension. So, after this finding, the patient could be classified as a pT3a. The pathologist also suggested that immunohistochemistry testing can be useful to better understand the exact subtype of cancer that caused that massive PSA level. This testing was not performed and the conclusion was drawn: adenocarcinoma of the prostate, poorly differentiated with a Gleason score of 9 (5+4).

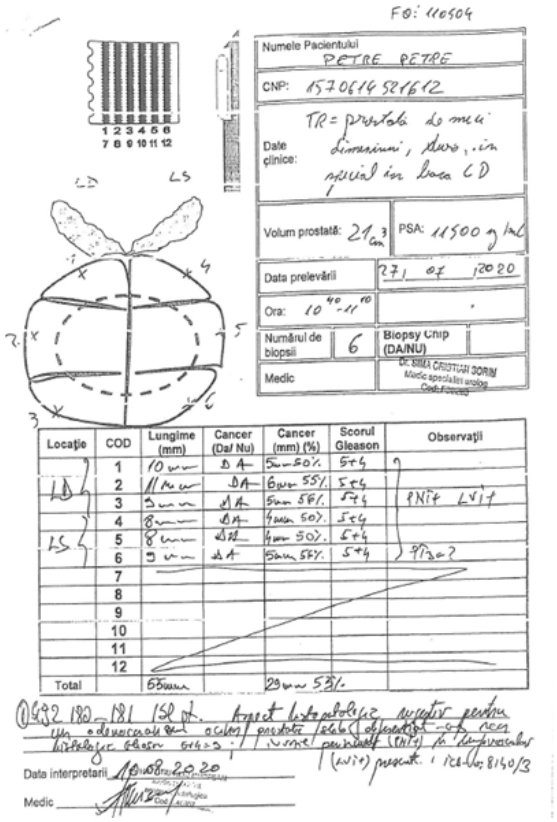


Fig. 5. Pathology report – all the fragments taken during the TRUS guided prostate biopsy were positive for malignancy – adenocarcinoma Gleason score 5+4 (patient's personal archive)

The urologist presented the results to the patient and recommended an oncological consultation as quickly as possible. In order to start the treatment faster, even before the appointment at the oncologist, the patient was advised to purchase a LHRH antagonist (Degarelix). He received 240 mg of Degarelix (initial dose).

RESULTS

Two weeks after the initial dose of Degarelix, he had a new PSA dosage which revealed a dramatic decrease, to a level of 1298 ng/mL from 11502 ng/mL. An increase in hemoglobin was also observed, from 8.6 to 9 g/dL. In light of these promising results and in the light of the data from the specialized literature that we will later develop in the "Discussions" part, a first urologist-oncologist discussion took place in August 2020. It was concluded that the patient has an indication for chemotherapy with Docetaxel and the continuation of the androgenic blockade, but with an LHRH agonist, in order to benefit from the National Health Insurance Fund. At that time, the patient presented an ECOg performance status of 1.

Thus, on 21.09.2020, the patient began treatment with Triptorelin 11.25 mg injectable every 84 days and Bicalutamide for 28 days (although the phenomenon of "flare- up" was highly unlikely). He also begins the first cycle of chemotherapy with Docetaxel, out of the six proposed. The second cycle is postponed due to pancytopenic adverse reactions caused by Docetaxel, more precisely thrombocytopenia 81000/μL and anemia 7.9 g/dL. After the hemoglobin increases, and with the help of a granulocyte growth factor, Pegfilgrastim, the patient resumes chemotherapy, completing all six cycles on 28.12.2020. The PSA decreased from 388 ng/mL after the first administration of Docetaxel, in September 2020, to a value of 218.3, then to 36.59, and after the fourth cycle it reached a minimum value of 16.93 ng/mL.

In January 2021, he performed a computed tomography with i.v. contrast substance. of the thoracic, abdominal and pelvic segments which reveals a stable aspect of bone metastases but the appearance of some pulmonary nodules, with a random disposition, the most about 3 mm apical right, which cannot be unequivocally described as visceral metastases, but in the given context not can be overlooked.

In another two months, on 01.03.2021, he performs a PSA in which an important increase is observed from 16.93 to 117 ng/mL. He receives the indication from the oncologist to perform a cerebral CT, which reveals the stationary nature of the bone metastases at the level of the skull, a slight cerebral atrophy and degenerative vascular lesions, but without cerebral metastases. At the same time, he performed a testosterone and a total PSA measurement. This analysis was relevant in showing that the total serum testosterone was kept at a castration level of 11 ng/dL and the PSA still rose to 144 ng/mL. This new analysis led to a change in the working paradigm, the prostate cancer evolving from the hormone-sensitive metastatic form to a metastatic castration-resistant prostate cancer (CRPC). It was decided that a new type of treatment was needed, with Enzalutamide, continuing also the androgen blockade with Triptorelin.

On 23.04.2021, the patient begins the treatment with Enzalutamide, and on 21.05.2021, he performs a first PSA dosage. A remarkable decrease is observed: from 144, the PSA dropped to 6.81 ng/mL; in July 2021 the decrease of the prostate antigen continues to a 1.75 value, and in October 2021 to 1.28 ng/mL. Unfortunately, this will be the lowest PSA value recorded, because after the first six-month series and the first month of the second series of Enzalutamide, the PSA would start to increase. It should be mentioned that the treatment with zolendronic acid was also initiated from July 2021. From an imaging point of view, the patient was stable and the ECOG performance status was still 0. At the end of the year, on 29.12.2021, a first increase of the PSA to 2.4 ng/mL was observed. After finishing the second series of 6 months of Enzalutamide, the PSA reached the value of 9.8 ng/mL. In July 2022, the PSA level was 46.5 ng/mL and testosterone immediately before taking Triptorelin was 55.41 ng/dL. The increase in PSA continued until the end of 2022, reaching 169 in September, and on 06.12.2022 reached a very high value: 3305 ng/mL, with a serum testosterone of 44 ng/dL. From a clinical point of view, the patient is stable, with a performance status on the ECOG scale of 0. Hemoglobin remains close to normal 11.9 g/dL despite the multitude of bone metastases (concentrated in hematogenous areas) in progression, detected at a bone scintigraphy performed on 12.12.2022.

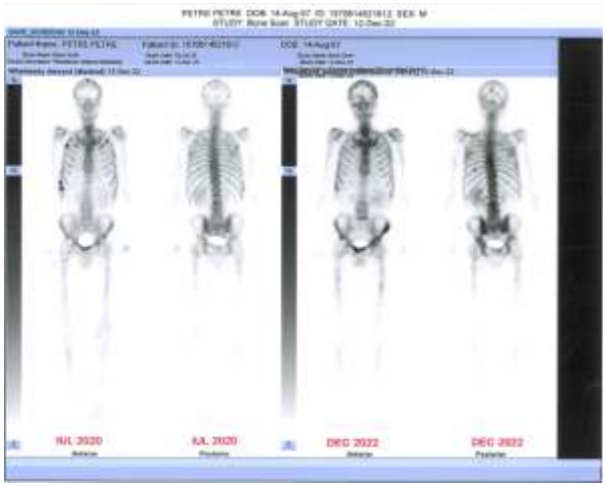


Fig. 6. Comparative study - two bone scintigraphs (29 months apart) which reveal an increase in the number of metastases, affecting vertebrae, pelvic bones, both acetabula and the left femur (patient's personal archive)

Arriving close to the present moment, we must say that the patient continues the treatment with Triptorelin, a true backbone of CRPC treatment, but stopped the treatment with Enzalutamide, starting a new cycle of chemotherapy with Docetaxel. On 20.12.2022, the first chemotherapeutic administration was performed for palliative purposes, the general condition and the paraclinical status allowing this. On 10.01.2023, the second dose of Docetaxel was administered, and the results will be analyzed from a biohumoral point of view.

DISCUSSIONS

Today's medicine is evidence-based medicine. Knowledge of clinical studies with a major impact on daily clinical activity is imperative, especially in a university clinic such as the "Prof. Dr. Th. Burghele" Urology Hospital. In what follows, I will present the main evidence from the specialized literature that was the basis of the clinical reasoning of the multidisciplinary urologist-oncologist team to change the treatment at the time when these changes occurred.

First of all, the decision from the initial moment to start androgen deprivation therapy with an LHRH antagonist must be discussed. The only drug approved for the treatment of prostate cancer in this class is Degarelix.[4] As stipulated in the European Prostate Cancer Treatment Guide, there is no evidence to prove the superiority of any method of castration: surgical (bilateral orchiectomy) or chemical (LHRH agonist or antagonist). However, if there is a situation that endangers the life and integrity of the patient with prostate cancer, such as compression of the spinal cord, then either bilateral orchiectomy or the LHRH antagonist is preferred. The explanation is that the two methods of treatment acts much faster, without the need to adapt testosterone production through the negative feed-back mechanism.[5] The urologist's reasoning at the time when he prescribed the initial dose of Degarelix of 240 mg was based on the consideration that the patient needs a treatment with fast action. Even without the result of the prostate biopsy, judging only by clinical considerations (rectal cough with hard prostate, fixed by the adjacent structures), imaging (CT of the chest, abdomen and pelvis with contrast material, ultrasound - large, hypoechoic nodule) and in especially paraclinical (PSA 11502 ng/mL and anemia suggestive of metastases in the hematogenous marrow) was considered at that time to be the best course for the treatment of a prostate cancer patient with a large volume of metastases.

Another component of hormone treatment in prostate cancer patients is the associated toxicity. It seems that LHRH antagonists and bilateral orchiectomy have a better cardiovascular safety profile than LHRH agonists, according to some recent studies.[6,7,8] This characteristic of LHRH antagonists becomes important, especially if we have to deal with a patient like the one we refer to in this case presentation, known with multiple cardiovascular comorbidities. Ultimately, the patient was treated with Triptorelin, an LHRH agonist, combined with Bicalutamide, an anti-androgen, although at that time the flare-up phenomenon seemed improbable. Regarding this flare up, opinions have been quite divided lately. Although in 1990 Thomson et al published data that incriminated the flare up (or Testosterone flare, T flare) in the case of some deaths[9], other authors contradict it.[10] The main reason for the switch from LHRH antagonist to agonist is but due to the health policies in Romania and the fact that the costs of the antagonist must be borne by the patient, while those of the agonist are borne by the medical care provider.

The most important step from the beginning of the treatment proposed to the patient when he was still in the stage of hormone-sensitive prostate cancer was the addition of docetaxel to the standard of care (SOC). Until recently, this compound was considered the first line of treatment for patients who show resistance to castration and must then switch to another form of treatment, more precisely chemotherapy. But in this era of great scientific effervescence regarding the progress in the treatment of prostate cancer, the therapeutic agents that until recently had a clearly established place in the treatment scheme, are now used with ingenuity for maximum benefit to the patient. A turning point in changing the conceptions related to the place of docetaxel was linked to the

publication of data from the STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy). In 2016, James and colleagues published an article in the prestigious journal The Lancet in which they demonstrated that the addition of Docetaxel from the beginning of treatment, in addition to SOC in patients for whom long-term androgen deprivation is indicated, brings a benefit in terms of survival, but with the disadvantage that it also produces more pronounced adverse reactions versus androgen deprivation as the only treatment. The conclusion was that Docetaxel should enter the SOC in a certain category of patients: men with high-risk, locally advanced, metastatic or recurrent prostate cancer, who start long-term first-line hormonal therapy. The same cannot be said about zolendronic acid, because it does not bring benefits in terms of survival, so it should not be added to SOC from the beginning of treatment.[11] The patient described in this case report perfectly fits the profile described by James and colleagues, a prostate cancer patient with Gleason score between 8 and 10, with PSA above 40 ng/mL, with de novo metastatic prostate cancer, naïve to treatment, in which long-term androgen deprivation is indicated.

After another three years from the publication in The Lancet of the article described above, in 2019, after a longer follow-up, Clarke and his colleagues reached the same conclusion: docetaxel added to SOC in patients with prostate cancer in the metastatic stage brings a plus in terms of survival regardless of the volume of metastases. That is precisely why the authors of the article plead for the early use of Docetaxel in these patients.[12]

Very useful were the articles based on the CHAARTED database (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer - E3805, ClinicalTrials.gov identifier: NCT00309985). More precisely, in the article published by Sweeney and his colleagues, it is unequivocally postulated that six cycles of Docetaxel at the onset of standard androgen deprivation in men with hormone-sensitive prostate cancer in the metastatic stage, brings clear benefits in terms of survival.[13] On the other hand, Harshman and her colleagues also discuss the nadir PSA cutoff in a statistical analysis of the CHAARTED cohort. It seems that a decrease in total PSA to a value lower than 0.2 ng/mL after 7 months of androgen deprivation is a favorable prognostic factor. A PSA nadir above 4 ng/mL was considered a negative prognostic factor. In Harshman's study, the conclusion was that hormonal treatment combined with docetaxel increases the chance of patients having a decrease in PSA below 0.2 ng/mL, and patients with a decrease in PSA have the best response to treatment and a longer survival. PSA below this value without the relief conferred by Docetaxel. It seems that this last conclusion was correlated with a smaller volume of metastases.[14] The patient whose case was presented in the Material and Method chapter, unfortunately the PSA decrease after Docetaxel treatment and Endogenic deprivation with Triptorelin stopped at 16.93 ng /mL. An explanation could be the large metastatic volume but also the aggressive behavior of the disease (Gleason score 5+4).

The next step in the patient's evolution was to change the treatment. This transition was made according to the oncological and urological treatment guidelines. It was decided to switch to treatment with Enzalutamide, a new generation antiandrogen, with a much more potent action compared to antiandrogens such as Bicalutamide or Flutamide. According to the European Prostate Cancer Treatment Guideline, the degree of recommendation to offer patients who have followed one or two lines of chemotherapy (Docetaxel, Cabazitaxel) Abiraterone or Enzalutamide is strong. Also, the guidelines state that it is necessary to switch to another line of treatment when the patient is fit. The decision was made to start treatment with Enzalutamide when the patient showed an increase in PSA from 16.93 to 144 ng/mL, but with an ECOG PS of 0. The PSA decrease was substantial after 7 courses of Enzalutamide, up to a minimum value of 1.28 ng/mL. This value from 11.10.2021 is the lowest, since the start of treatment on 27.07.2020. Unfortunately, from this moment the trend was of continuous growth. At the present moment, as previously noted, the patient is again undergoing treatment with Docetaxel. This approach is in accordance with the European Guideline for the Treatment of Prostate Cancer which strongly

recommends switching to Docetaxel in patients who were previously treated with Abiraterone or Enzalutamide when the evolution is not favorable.

It should be mentioned that the patient also received treatment with a bisphosphonate three months after the start of treatment with Enzalutamide, more precisely zolendronic acid administered once every 3 months, from 22.07.2021 (seven administrations, in March he is scheduled for the eighth administration).

CONCLUSIONS

The evolution of the patient whose case was presented above proves how much the treatment options have evolved for the patient diagnosed with prostate cancer in the metastatic stage. Also, we can see that nowadays a multidisciplinary team is needed, often consisting of Urologist, Anatomopathologist, Oncologist, Radiotherapist, Assistants, Specialist in Palliative Medicine, Cardiologists, Psychologist, etc. We must not forget that most of the time family support is of great importance. The effort to follow treatments, with adverse reactions hard to bear, to carry out clinical, laboratory and imaging investigations, with a draconian regularity, proves to be almost impossible to complete without help. These patients have a reduced performance status and often complain of pain due to metastases.

It is necessary to know how to recognize the moment when we have to change the treatment. A great advantage is communication with an oncologist who can closely follow the evolution of prostate cancer, recognize the moment when it becomes resistant to castration and act accordingly. Knowledge of treatment guidelines, the latest trends in oncological treatment, clinical studies that have the potential to change the way of action in clinical activity and, last but not least, a real interest of the modern urologist in oncology are important. The importance is given by the dynamics of the current medical and academic ecosystems, which forces the urologist to be multidisciplinary in order to have a common language with the oncologist.

Regarding the actual case of the presented patient, we must once again note the huge value of the PSA, 11502 ng/mL, the aggressiveness of the prostate cancer, with a Gleason score of 9 (5+4), but also the multitude of treatments that the patient benefited. The patient's evolution will continue to be followed closely and the results will be published in another article.

Acknowledgement. The authors wish to express their gratitude to the patient and the patient's family for the agreement given to disclose information related to the state of health, the evolution following treatments and all investigations carried out.

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