Surgical Complete Androgen Blockade (SCAB) in the prostate cancer: A treatment from the past with future perspectives

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Abstract: The dependence of prostatic cell from androgens is widely known. Until recently, the dominant belief was that the complete androgen blockade of the cancerous prostatic cell was successfully achieved by drugs and for that reason, the unresponsive to hormone treatment disease was characterized as “hormone refractory prostate cancer” or “hormone resistant”. However, over the last years, modern endocrine, biology and pharmacology, through clinical trials, concluded that pharmaceutical androgen blockade is not as complete as we considered it to be. As result of this conclusion, the modern term is “castration resistant prostate cancer” (CRPC) in contradistinction with “hormone refractory prostate cancer”. The present paper analyses and explains the steroidogenesis cascade of androgens and their interaction pathways with the prostatic cell. Likewise, the basic pharmaceutical hormone manipulations in metastatic prostate cancer are mentioned and the causes of their deficiency in achieving complete androgen blockade are explained. Also, Surgical Complete Androgen Blockade (SCAB) is analysed in detail and a modern application of this alternative therapy is proposed. Furthermore, based on statistics, the advantages regarding the estimated cost of the SCAB are elaborated as opposed to the pharmaceutical cost in Greece. In addition, powered by facts from the past and the present, a safe trial of SCAB is proposed on selective patients in terms of a modern investigational protocol.

Key words: prostate cancer, hormone therapy, androgen blockade, bilateral adrenalectomy, androgen receptors.

Introduction
In Europe, prostate cancer is the most common type of solid neoplasm with an incidence of 214 cases per 1000 males¹. It also constitutes the 2nd most common cause of death (COD)
from cancer in males\(^2\). The close relation of the prostate gland with the testicular function was perceived at the end of the 19\(^{th}\) century by J.W. White who, in 1893 in Philadelphia, suggested the orchiectomy in men with prostatic hyperplasia\(^3\). In 1941, C. Huggins established the major dependence of the prostatic cell from androgens and made the following statement: "It is now perceived that racial hormones affect certain types of cancers. The impact may be manifested either as acceleration or retardation of their progress. So, the androgens seem to accelerate the progress of prostate cancer and the oestrogens retard it". (C. Huggins, 1941)\(^4\). To the present day, endocrine has, to a certain degree, elucidated the way in which the androgens interact with the prostatic cell. It seems that the blockade of androgen production and their interference with the androgen receptors (ARs) of the prostatic cell are the primary factors in the prostate cancer’s hormonal control.

**The role of the Androgen Receptors (ARs)**

ARs are localized inside the prostatic cell’s cytoplasm, bound to heat shock proteins (HSPs) unable to bind to DNA. They are activated after binding androgens and translocate to the nucleus of the prostatic cell inducing DNA transcription and replication, RNA action with gene transcription and eventually cell proliferation\(^5\). Hormonal manipulations aim to block these effects of the ARs and subsequently inhibit uncontrolled proliferation of the prostatic cells. The main way to achieve it is the blockade of the ARs from the androgens activating them.

**The steroidogenesis cascade of androgens**

Androgen production starts at the mitochondria of the Leydig cells of the testis and the endocrine cells of the adrenal cortex by converting acetic acid to cholesterol and then to pregnenolone by desmolase enzyme (C20-22 lyase). Pregnenolone is converted to progesterone and by 17-alpha-hydroxylase CYP17 to 17OH pregnenolone and then to dehydroepiandrosterone (DHEA). by the enzymatic activity of 17-alpha-hydroxylase, progesterone in the Leydig cell is converted into 17-OH progesterone and by C 17-20 lyase of the CYP17 to androstenedione (AED). DHEA also converts to androstenedione by 3BHSD-1. However, in the adrenal endocrine cell, the progesterone can follow another metabolic pathway and convert to corticosterone (CORT) and eventually to aldosterone (Fig. 1).

DHEA is the first androgen formed in the chain of enzymatic reactions. It converts to AED and this in turn converts by 17-ketoreductase to testosterone (T). By 5-alpha reductase (5-AR), testosterone eventually transforms into the most active molecule, dihydrotestosterone (DHT). Androstenedione, testosterone and dihydrotestosterone are able to associate with ARs, activating them for prostatic cell proliferation. Moreover, a close relation of mutant AR types resulting in their activation by DHEA has been observed in vitro \(^6,7\).
The effect of modern drugs in androgen blockade

In the treatment of metastatic prostate cancer, the urologist’s primary goal is to stop the proliferation of the cancer prostatic cells. The main way to attain it is to deprive ARs from the androgens activating them. The urologist’s armory in clinical practice includes:

**Luteinizing hormone-releasing hormone (LHRH) analogs** (busereline, goserelene, leuprorelene, triptoreline): They induce pharmaceutical castration by acting as negative feedback to the hypothalamic-pituitary system and causing the reduction of LH secretion from the anterior lobe of the pituitary resulting in the abrogation of steroidogenesis in the Leydig cells.

**LHRH antagonists** (abarelix, degarelix): They directly bind and deactivate the LHRH receptors in the anterior lobe of the pituitary by blocking the LH secretion; the result is comparable to that of the LHRH analogs.

**Antiandrogens** (bicalutamide, flutamide, nilutamide, cyprotero-ne acetate, megestrol acetate, enzalutamide, RD162): They act directly on ARs, obstructing their binding with the androgens that continue to synthesize in the adrenal cortex, given that LHRH analogs and LHRH antagonists target solely the testicular Leydig cells. The combination of antiandrogens and LHRH analogs or LHRH antagonists is called maximum or complete androgen blockade (CAB).

**Oestrogens** (Diethylstilboesterol-DES): They also lead to negative feedback to the pituitary and the outcome is respective to that of the LHRH analogs or LHRH antagonists but with increased risk of cardiovascular events.

**Abiraterone**: It binds with CYP17 and deactivates it. Its primary goal is to stop the androgen biosynthesis cascade after the pregnelone and progesterone stage. It acts both on the adrenal synthesis of androgens as well as on the Leydig cell.

**Ketoconazole**: It is an antifungal agent that inhibits various enzymes of cytochrome P450, including CYP17. Its action is analogous to abiraterone but with less specificity and weaker affinity to CYP17 and thusly, reduced effects compared to abiraterone.

**Reasons behind medication insufficiency in managing SCAB**

The discovery of CYP17 inhibitors action such as abiraterone, pregnane and androstane caused the term of the formerly known as “hormone refractory prostate cancer” to change into “castration resistant prostate cancer” (CRPC) given the establishment that despite its progress under castration, it continues to respond to hormonal manipulations for the reduction of androgens production. The above was confirmed by the clinical efficacy of abiraterone use which was documented by the increase of the overall survivorship (OS) in CRPC patients. However, the disease progress, albeit the stopping of steroidogenesis, beyond the stage of pregnenolone and progesterone, means that there are other AR
activation pathways as well. It has been showed that certain AR mutations contribute to their inability to be deactivated by the antiandrogens and to be activated by progesterone and oestrogens or even by the antiandrogens themselves\textsuperscript{13,14,15}. Also, in patients with castration levels of serum testosterone, androgens are detected within the prostatic cancer cells at a rate of 10-25\% of the respective androgenic patients who receive no treatment. These androgen levels can activate the ARs and result to gene expression and cellular proliferation\textsuperscript{16}. The androgens, including testosterone, derive from de novo synthesis from progesterone and the conversion of AED within the prostatic cell\textsuperscript{17}. Androgens are also produced by progesterone in the Setoli cells of the testes\textsuperscript{18}. It is thusly concluded that steroids comprising precursor molecules for the formation of androgens, act directly as androgens on the prostatic cancer cell. Progesterone is their primary representative.

Progesterone is a steroid which forms by pregnenolone in the mitochondrion of the Leydig cell and the adrenal cell. To up to date hormonal therapeutic manipulations do not affect the synthesis of this significant steroid which has the property of directly and indirectly enhancing the prostatic cell proliferation. Abiraterone, acting at a higher level compared to any other substance on the steroidogenesis cascade, acts against 17-alpha-hydroxylase and C17- 20 lyase – enzymes belonging to CYP17 of cytochrome P450 and are traced in the endoplasmic reticulum (ER). The result is that pregnenolone and progesterone synthesize in the mitochondria but are not affected by abiraterone. Modern endocrine has proven that
the so-called “hormone refractory prostate cancer” is initially castration-resistant and that the adrenal steroids continue to act upon the prostatic cancer cell. Surgical removal of the androgen production sources constitutes a way of complete deprivation of ARs from androgens. This is achieved by bilateral orchiectomy and synchronous bilateral adrenalectomy and is called SCAB.

**SCAB: A safe and effective treatment**

Orchiectomy for castration purposes in managing the prostatic cancer cell has been known since the 18th century and is safely performed within a few minutes. Bilateral adrenalectomy in prostatic metastatic cancer was first carried out by the gifted Huggins, though the outcomes were disappointing due to acute adrenal deficiency; cortisol had not been discovered at the time19. But with the discovery and use of acid cortisone, the procedure came back to the fore and, in 1960, Mac Farlane et al. published his patients’ OS, the maximum being 46 months20. Seven years prior to Mac Farlane, Taylor had announced that out of 6 patients with prostatic metastatic cancer, who were managed with adrenalectomy, 5 exhibited subjective improvement and 3 objective. In particular, leukocytes patients were able to mobilize shortly after the procedure. The objective improvement was recorded as reduction in acid phosphatase values, decrement of the prostate size which at the same time became flaccid, lower limbs detumescence, osteoblastic lesions reduction shown in radiologic studies and body weight increase21. In 1974, Bhanalp et al., also reported objective remission of osseous metastases and alcalic phosphatase levels subsequent to bilateral adrenalectomy in metastatic prostatic cancer22. Finally, the same year, Merrin published an article for a stage D patient manifesting metastases even on the perineal skin, who was tumor-free 4 years after the bilateral adrenalectomy23. Today, bilateral adrenalectomy can be performed laparoscopically; mean operative time 308 minutes (190-440 min), mean blood loss 138 ml (30-300ml). The access is transperitoneal in flank position and postoperatively, the patients are daily administered hydrocortisone and fludrocortisones as restoration treatment due to their adrenal deficiency24. Furthermore, a retrospective study of 30 patients who had undergone synchronous laparoscopic bilateral adrenalectomy with no intraoperative complications and mean postoperative hospitalization 3.5 days concluded that, combined with glucocorticoids and metalocorticoids administration, it constitutes a safe method as restoration treatment under endocrine monitoring25. The same conclusions were reached by Castillo after 22 synchronous laparoscopic adrenalectomies that he performed in less than 210 min; mean blood loss 63ml, mean hospitalization 3.2 days26. With regard to OS of patients who were subjected to bilateral adrenalectomy, most information comes from the past, when the procedure comprised the main treatment of the Cushing syndrome. In a retrospective study, from 1953 to 1980, it is reported that 79 patients who had undergone open bilateral adrenalectomy, their 20- and 5-year survivorship reached 62 and 79%, respectively27. The rates are
particularly encouraging if we consider the means of endocrine monitoring and infection management of the time. Also, in 1997, a published case report described the case of a patient who, having undergone synchronous bilateral adrenalectomy for the resection of adrenal metastases because of lung cancer, received cytotoxic therapy and was disease-free for more than 9 years.

The involvement of adrenal androgens in the progress of prostate cancer was perceived a long time ago, but now the clinical importance of the deprivation of the prostatic cell from them has been also established. The main proof is the prolongation of OS by abiraterone, which inhibits the steroidogenesis cascade of the androgens. Yet, there are still no medication inhibiting the biosynthesis of all steroids inducing prostatic cells proliferation directly or indirectly. Such a precursor steroid is progesterone. Bilateral adrenalectomy and synchronous bilateral orchiectomy would instantly deprive the prostatic cancer cell from all the steroids with potent androgenic properties and would result in the stopping of the proliferation and eventually to apoptosis. Laparoscopic bilateral adrenalectomy is the procedure with few complications and less postoperative hospitalization. Furthermore, the simplicity of bilateral orchiectomy is established for many years now. The OS in patients who had undergone synchronous bilateral adrenalectomy was significantly long in older trials despite the absence of current endocrine knowledge and modern therapeutic substitutions.

As for the adrenalectomy attempts in patients with metastatic prostate cancer, these were performed when neither CT and MRI scans and bone scintigraphy nor PSA test or the Gleason grading system were available. The patients managed with those pioneering procedures were of terminal stage and the only means available for diagnosis and surveillance of the disease were clinical examination, acid phosphatase and plain x-rays. Contemporary methods of early diagnosis and prostate cancer surveillance in combination with advanced surgical techniques, serve for new perspectives in the application of early SCAB. Also, the existing chemotherapy drugs (docetaxel, mitoxantrone, estramustine, cisplatin, carboplatin) are not ruled out from the treatment scheme. A strategic application of cytotoxic therapy could be its immediate administration secondary to the patient’s full recovery. Thusly, the patient would receive the greatest reduction in cancer burden for healing purposes. Another strategic application of cytotoxic therapy could observe current data by applyign it when prostate cancer is hormone-resistant. Finally, this new cancer treatment version does not exclude supportive care with diphosphonic acids or radionuclides. Even the use of abiraterone as a second- or third-line drug, would possible have a point because it has been shown that even within the prostatic cancer cell, it is possible to have androgens synthesis from substances like cholesterol with CYP17 involvement.
**Cost-effectiveness of SCAB**

The lack of statistics on prostate cancer in our country is an obstacle in the accurate estimation of the economic benefit the application of the method would have. The only statistical information that exists is that in Greece, 2,412 men are diagnosed with prostate cancer annually. According to the American National Cancer Institute (NCI) Cancer Center Program (Surveillance, Epidemiology, and End Results (SEER) Program), in the 4% of newly diagnosed prostate cancer in white males, the disease is not local. If we apply this information to the disease incidence in our country, we will see that approximately 100 patients are candidates for hormonal therapy. From them, the highest rate will have 5-year survivorship since the rates for N+ and M+ disease are 100% and 27%, respectively (SEER) with M+ falling short of the N+ disease at the time of the diagnosis. The annual CAB cost can be easily estimated by summing up the annual cost of daily bicalutamide intake (50 mg/per day X 45 euros X 12 months = 540 euro) and the annual cost of the LHRH analog. For example, Triptorelline/11.25mg, is administered every trimester and costs 247 euro X 4 trimesters = 988 euro per year. So, the annual CAB cost amounts to approximately 1,529 euro. The respective amount for a 5-year period is estimated at 7,640 euros per patient. Therefore, for the 100 new patients per annum the cost is 764,000 euro. According to the Diagnosis-related groups (DRGs) of the Greek Ministry of Health and Social Solidarity, the adrenalectomy costs 3,000 euro and the orchiectomy 300 euro. It is understood that the respective cost of a 5-year treatment plan with SCAB for 100 new patients amounts to 330,000, i.e. 2.3 times smaller compared to pharmaceutical CAB. The cost-effectiveness is even greater if we also consider the number of patients who are not included in any statistics and those who proceed with cytotoxic or abiraterone therapy, the cost of each amounts to 3,500 euro per month per patient. As for enzalutamide, a new molecule with antiandrogenic effect (acts against ARs) is still under investigation and costs approximately 150 euro/10mg; the daily dose used in clinical trials ranges between 30mg to 240mg, i.e. 450 to 1,000 euro per day. Accordingly, the monthly enzalutamide treatment is estimate at 13,500 to 30,000 euro per patient. Outpatient follow ups, laboratory surveillance cost and therapy-induced complication treatment costs were not included in the above estimations.

**Conclusions**

SCAB within the framework of a modern research protocol would offer valuable information for the actual impact of the androgens in the progress of the disease. Also, in case of successful outcomes, it would constitute an economic approach in the effective treatment of metastatic patients, given the cost, apart from the procedure, is limited only to glucocorticoids and metalocorticoids intake which are of very low cost and the follow up which is burdened by the endocrine monitoring.
The modern trend of replacing the term “hormone refractory prostate cancer” with “castration resistant prostate cancer” (CRPC) is a consequence of the establishment that the prostatic cell should be 100% free from androgens before we use the term hormone-resistance. Current therapy seems inadequate to achieve this goal. SCAB is possibly the most effective and simultaneously the most economic method for maximum deprivation of the prostatic cancer cell from androgens and steroids with mitotic effect on it. With respect to the conditions under which it was tested in the past, the result at that time and the contemporary progress in surgical techniques, endocrine, pharmaceutical and laboratory support and the advancements in diagnosis and monitoring of prostate cancer from the modern urologist, we conclude that today, in terms of a research protocol, it could constitute a safe intervention with maximum oncologic benefit in certain patients.

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