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Bipolar Androgen Therapy in the management of prostate cancer

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Abstract

Introduction and purpose: Prostate cancer (PCa) as one of the most frequent neoplasms in men remains a challenge for oncologists. The main strategy of its treatment is the Androgen Deprivation Therapy (ADT) the principle of which is an inducement of hypogonadism. The lack of testosterone is not only a factor greatly contributing to a decrease of quality of life overall, but additionally it increases the odds of the complications, including low libido and erectile disfunction, metabolic abnormalities, high cardiovascular risk, osteoporosis, anaemia, or depression. ADT also has the potential of inducement of castration resistance (CRPC), which significantly worsen patients prognosis. The main purpose of this review is to explore the Bipolar Androgen Therapy (BAT), which has the potential to solve the aforementioned problems.

State of knowledge: The mechanism of BAT action has been described. BAT is effective not only against CRPC, but androgen-dependant PCa as well. BAT reverses the hormone resistance in CRPC, thus allowing the rechallenging of the ADT. It has the direct cytotoxic effect on cancer cells. Additionally BTA increases the exponents of the general quality of life of the patients. There is a number of active clinical trials regarding BAT.

Conclusions: BAT is a safe therapeutic strategy with the high efficacy in reversing hormone resistance in CRPC patients, thus significantly increasing their health prognoses and it allows to alleviate or avoid the adverse effects of ADT.

Key words: Bipolar Androgen Therapy, prostate cancer

Introduction and purpose

Prostate cancer is a major cause of mortality in men, ranking as the second most common cancer and the fifth leading cause of cancer death in men. According to GLOBOCAN 2020 an estimated 1.4 million new cases reported in 2020. The use of agents that block the androgen pathway (androgen-dependent therapy) is the current treatment for prostate cancer. When resistance to this treatment develops it leads to primary castration-resistant prostate cancer (CRPC) or to metastatic CRPC. Hormone-resistant prostate cancer is defined by disease progression despite castration-resistant serum testosterone levels. CRPC develops within 5 years in 10-20% of patients with metastatic prostate cancer. From the onset of resistance, median survival is approximately 14 months (1). Until recently, taxane-based chemotherapy was the mainstay of treatment for patients with advanced metastatic prostate cancer who had disease progression despite maintaining castration-based testosterone concentrations. A better understanding of the mechanisms in the acquisition of castration resistance has given prostate cancer new, effective therapeutic options. The standard treatment for patients with metastatic hormone-sensitive prostate cancer is combination systemic therapy - standard androgen deprivation therapy (ADT) and abiraterone acetate with prednisone or docetaxel (2). Various treatment strategies are used in patients with CRPC i.e. surgery, radiotherapy, chemotherapy and ADT. ADT may consist of surgical castration, treatment with luteinizing hormone-releasing hormone (LHRH) agonists that lower the amount of testosterone or anti-androgens connecting to androgen receptors keeping the androgens from causing tumor growth (3). Phase III clinical trials have confirmed the effectiveness of treating patients with castration-resistant prostate cancer with novel hormonal therapies using abiraterone acetate (4).

Historically, testosterone was considered to be one of the direct factors causing the increase of the CaP risk most of the time (5). Work of Huggins et al. (6) was the first to show cancer regression in response to castration, and other animal and *in vitro* studies (7,8) gave similar results. In that way, this androgen-dependent CaP model became a basis of CaP therapy, which became focused on anti-androgen action, e.g. castration, or pharmacologically lowering the production of dihydrotestosterone (DHT) (9). This approach isn't devoid of problems though. One of them is that the hypogonadism caused by antiandrogenic therapy is a very serious side effect, which can cause a significant decrease in patient's quality of life, due to low libido and erectile dysfunction, metabolic abnormalities, higher cardiovascular risk, osteoporosis, anaemia, or depression. The more dangerous, possible repercussion of antiandrogen therapy is the castration resistance which indicates the independence of the tumour from systemic testosterone in response to the therapy, thus making it useless and

worsening the patient's survival prognosis. The above problems aroused interest in the possibility of abandonment of androgen deprivation. Some studies (10–12) showed the lower risk of recurrence and less aggressive cancer in patients with relatively higher testosterone levels. According to some observational studies (13,14) the testosterone replacement therapy was proven to be safe, or even to lower cancer risk in patients treated with it. Unfortunately, an abundance of data still indicates testosterone suppression as a successful strategy. The Bipolar Androgen Therapy (BAT), which combines the features of the two aforementioned approaches, may be the intensely sought effective compromise. The main BAT premise is cycling between supraphysiological and ablative concentrations of testosterone by pharmacological (or surgical, which is rare) castration, and cyclic testosterone supply in such time intervals, that allows the decrease of testosterone back to castrate levels. The main purpose of this review is to explore the BAT, which has the potential to not only reverse the castration-resistance, but to act as a cytotoxic agent against cancer cells and improving the quality of life of the patients.

The state of knowledge

The mechanism of action

BAT works on the principle that one of the characteristic features of castrate-resistant prostate cancer (CRPC) is overexpressed androgen receptors (AR) in the purpose of adaptation to low levels of androgens. High concentration of cells AR and possible mutations in its structure renders them immune to a deficit of its ligands, allowing cancer cells to thrive without hormone, making androgen deprivation therapy (ADT) futile (15). Therefore it is thought that cycling between supraphysiological and subphysiological levels of testosterone can, at first saturate AR, halting degradation of receptors, which inhibits progression of cell cycle and prohibits its division. In the testosterone deprivation phase, cancer cells that downregulated their AR are once again susceptible to low levels of androgens (16).

It was proven that increased expression or activation of an AR can lead to growth inhibition, due to several factors. Arrest in the G0/1 phase of the cell cycle is a result of increased expression of cyclin-dependent kinase inhibitors p21 (p21cip1) and p27kip1, with suppression of p45/SKP2, a molecule that targets aforementioned inhibitors to proteasomal degradation (17–19)While in androgen-sensitive cells testosterone is considered as an anti-apoptotic factor, it can induce apoptosis in CRPC cells (20). Lin et al. showed that castration-resistant cell line, the AR promoted B-cell lymphoma 2 associated x, apoptosis regulator (BAX) expression, that eventually led to apoptosis (21). Additional featured functions are disruption of DNA licensing, which results in impaired DNA synthesis (22); repressed transcription of AR gene (23); and induced damage to the cellular dsDNA, sensitizing cell to testosterone therapy and antineoplastic agents (24).

Finished clinical trials

In a 2015 pilot clinical study, 16 asymptomatic patients with metastatic CRPC were treated. On day 1 out of 28 they were given 400 mg of testosterone cypionate intramuscularly, additionally they were treated with etoposide on days 1-14 of 28. 5 out of 10 patients eligible for evaluation showed radiographic response to the therapy, PSA levels in 7 of them got significantly decreased. (25)

Sena et al. in 2021 presented the results of a multi-kohort study with 29 patients with CPRC. As a result of cycling testosterone levels in BAT 17 of 18 patients achieved a 50% reduction in PSA levels. After progression, the abiraterone or enzalutamide turned out to be effective again – 90% reduction of PSA was observed. (26)

The RESTORE study at Johns Hopkins Hospital included 59 patients with metastatic CRPC-29 after abiraterone and 30 after enzalutamide treatment. They were given 400 mg of testosterone cypionate every 28 days with a luteinizing hormone antagonist treatment. After progression in time of BAT treatment, AR antagonists were restarted. In response to BAT and AR-targeted therapy, a decrease in PSA of more than 50% from baseline was observed. The PSA50 response to AR retreatment was higher with enzalutamide than with abiterone and also higher compared to BAT without AR therapy. BAT also showed the ability of resensitising cancer cells to the androgen deprivation therapy. (27)

Other benefit of BAT treatment is the improvement of the general quality of life, and general health. Schweizer et al. included in their study asymptomatic patients with a low or no metastases. After 6 months of androgen deprivation therapy (ADT), those patients who had a PSA <4 ng/ml, received BAT and deprivation therapy cycles which lasted 3 months. BAT therapy was applied on days 1, 29, 57 as intramuscular testosterone, cypionate or enanthate at a dose of 400 mg. ADT was used through the whole study. The usage of BAT turned out to be associated with the loss of subcutaneous and visceral fat, and significant gain of muscle mass. Overall quality of life rose as well (28).

Unfinished clinical trials

Despite the wide variety of studies which have ended, there are some ongoing trials. One of them (NCT04424654) the second phase study enrols the patients who suffer from castration-resistant prostate cancer and their previous treatment included androgen deprivation therapy and androgen receptor targeted therapy. The intramuscular (IM) testosterone cypionate 400 mg is given to the patients every 28 days. The three cycles are performed. The analysis will be based on patients tests such as plasma which will be collected for cell-free tumour DNA analysis as well as CTC ARV7 status and 68 Gallium-PSMA PET. Another second phase study (NCT02090114) registered 110 patients who progressed on androgen ablative therapy and on prior treatment with enzalutamide and abiraterone acetate + prednisone. The measures of primary outcome include the level of PSA as a response to BAT as well as response to enzalutamide, abiraterone or castrate levels of testosterone after BAT. In one of the studies (NCT01750398) results showed that 17 participants out of 29 met the primary outcome, which is PSA <4ng/mL at the end of the study, after BAT.

The next trial (NCT02286921) compares the effectiveness between BAT and standard therapy, which is enzalutamide. Participants are men with asymptomatic progressive metastatic castration-resistant prostate cancer. The BAT therapy consists of 400mg of testosterone cypionate or testosterone enanthate given every 28 days. The primary outcome is: progression free survival as measured by months until clinical or radiographic progression. The time frame is up to 2 years. The results showed that the median time of progression free survival is 5.62 months for BAT and 5.72 months for enzalutamide.

There are some studies that reveal the combination of BAT and other drugs, such as nivolumab. The study (NCT03554317) enrols men with progressive prostate cancer whose

previous therapy consisted of gonadotropin-releasing hormone analogues. Patients will be treated with testosterone cypionate 400mg IM every 4 weeks for the 12 weeks. After that time nivolumab 480mg intravenously (IV) will be administered every 4 weeks. The testosterone will be maintained every 4 weeks. The therapy will last 3 months. The primary outcome will be measured by PSA response to BAT + nivolumab. BAT will be tested (NCT04704505) with Radium-223 (RAD) in patients with progressive, metastatic prostate cancer as well. The dose of RAD will be 55 Kilobecquerel per kilogram of body weight IV every 28 days for 6 cycles. The testosterone cypionate 400mg will be administered every 28 days as well. The primary outcome is based on radiographic progression-free survival of BAT-RAD therapy. The next study (NCT04558866) enrols patients with progressive prostate cancer, after the abiraterone treatment. The men will be given extreme BAT which consists of darolutamide 1 200mg/day per os for 28 days with testosterone cypionate 400 mg IM. The radiographic progression free-survival rate will be measured. Carboplatin AUC 5 will be checked with BAT (500mg of testosterone enanthate) as well. The primary outcome is measured by PSA response rate.

Conclusions

BAT is a safe therapeutic strategy with the high efficacy in reversing hormone resistance in CRPC patients, thus significantly increasing their health prognoses and it allows to alleviate or avoid the adverse effects of ADT.

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