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Prospect and current situation of ADT drugs in the treatment of prostate cancer: towards combination therapy

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ABSTRACT
At present, people's research on prostate cancer is no longer limited to simple single-agent ADT therapy, to dual therapy, and then to the gradual maturity of triple therapy, and now it is more inclined to be used in combination with chemotherapy drugs, immunosuppressants or some new endocrine drugs. However, there are still a large number of side effects of related drugs, and they are still in the stage of clinical testing or theoretical research, and have not yet entered the stage of clinical application. At this stage, there are still certain limitations in the development of ADT drugs and their combination medications, but the existing combination drug regimens have provided patients with a relatively rich drug regimen.

KEYWORDS
ADT; combination therapy; prostate cancer

1 Current status of prostate cancer therapy

Prostate cancer is the second most common cancer in men, accounting for 7% of all newly diagnosed cases in men [1]. According to data statistics, with the further economic development of a country or region, the incidence of prostate cancer in the local area will also increase. The carcinogenesis process of prostate cancer follows a multi-step process, with prostate epithelial neoplasia appearing first, followed by localized prostate cancer. When the condition has further deteriorated, it would evolve into locally invasive advanced prostate adenocarcinoma, and eventually formed metastatic prostate cancer [2]. In general, prostate carcinogenesis is caused by a variety of mechanisms: unhealthy diet, like high-fat intake, which can increase the secretion of pro-inflammatory factors (such as IL-6) in the body, thereby affecting hormone metabolism and causing overexpression of androgens, which in turn leads to prostate cancer [3]; Hereditary prostate cancer caused by changes in DNA damage repair pathways, resulting in the inactivation of some tumor suppressor genes and the inability to complete some gene repair [4]; Epigenetic changes in some cancerous tissues of the prostate, such as abnormal DNA methylation and dysregulation of histone modifications, lead to inhibition of tumor suppressor gene expression and high expression of tumor progene . Currently, in the early stages, the primary treatment is radical resection directly targeting small tumor portions; in the intermediate stage, this is generally combined with radiotherapy. In the late stage of prostate cancer, control is mainly achieved through medication. The most commonly used and best treatment drugs for castration-resistant prostate cancer are abiraterone and enzalutamide. For specific gene mutations, the optimal approach is generally a combination of immunotherapy. For metastatic castration-resistant prostate cancer, the treatment primarily involves a regimen combining ADT medications with chemotherapy. Although there are so many mechanisms that lead to the process of prostate cancer, different mechanisms have different medications for targeted treatment. The treatment of prostate cancer is based on ADT therapy, followed by new endocrine drugs, chemotherapy drugs, and immunosuppressants as adjuvant or combination regimens.

2 Overview of ADT

ADT (androgen deprivation therapy) inhibits the growth of cancer cells by lowering the level of androgens (such as testosterone) in the body or blocking their effects. At this stage, it mainly includes four major types of drugs, LHRH agonists, LHRH antagonists, androgen receptor antagonists and androgen synthesis inhibitors, of which the first three are traditional ADT drugs, and the last androgen synthesis inhibitor is a new type of endocrine therapy drug. Of course, some other drugs, such as diethylstilbestrol, have been used sparingly due to their greater cardiovascular risk. LHRH agonist drugs mainly promote the secretion of related hormones by binding to LHRH receptors in the pituitary gland, promote a transient increase in testosterone or estrogen, and after a period of medication, the pituitary receptors are inhibited, eventually causing the level of sex hormones to drop to castration levels. Its main drugs include leuprolide and goserelin. However, LHRH antagonists mainly directly inhibit the secretion of related hormones by directly binding to LHRH receptors, so as to achieve castration levels. Its main representative drugs include degarelix and the latest drug relugolix.

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Androgen receptor antagonists block interactions with DNA primarily by binding to AR while preventing AR from the cytoplasm to the nucleus. [5] Its representative drugs include the first-generation bicalutamide, the second-generation enzalutamide, etc. The newest type of ADT drugs is Androgen synthesis inhibitors, which mainly act on CYP17A1 enzymes to block the synthesis of androgens in the adrenal glands and tumors [6]. Furthermore, many researchers now prefer to conduct combination therapy trials using Abiraterone and Enzalutamide along with various other types of medications. ADT treatment has evolved from a single use medication at the beginning, to combination medication in double, and then to the current research on combination medication in triple. However, it can still cause some side effects, particularly those associated with typical chemotherapy-related (neutropenia) and ARTRA-specific side effects. Among them, dual therapy regimens generally have fewer side effects compared to monotherapy regimens, and their efficacy is also superior to that of the latter. In contrast, triple therapy regimens do not show a significant reduction in side effects compared to dual therapy regimens; rather, their advantages are more evident in terms of efficacy, with improvements observed in pharmacokinetics and therapeutic index compared to dual therapy.

3 Combination of ADT drugs and new endocrine drugs

Essentially, new endocrine drugs are developed on the basis of traditional ADT drugs. Furthermore, in this type of combination therapy, most combination regimens involve pairing two of the four types of ADT drugs, and even combinations of three types of medications. So their mechanism and side effects are similar to that of traditional ADT drugs.

3.1 Regimens of enzalutamide in combination with ADT drugs

In a randomized study about enzalutamide or placebo plus leuprolide acetate and enzalutamide monotherapy in high-risk biochemical recurrent prostate cancer, participants were given 160 mg/day of enzalutamide per day, and the experimental group was required to take an additional 22.5 mg/12 weeks of leuprolide acetate (LA), which showed better risk of PSA progression compared with enzalutamide alone and metastasis-free survival (MFS) [7]. Therefore, this treatment regimen has a certain viability for patients with this type of prostate cancer in terms of long-term medication to suppress the metastasis and recurrence of prostate cancer.

Table 1 Statistical results after 60.7 months of follow-up.

	MFS	Risk of PSA progression
Monoenzalutamide regimen	HR 0.63;95% CI 0.46-0.87;p=0.049	HR 0.33; 95% CI 0.23-0.49; p<0.0001
Combination regimens	HR 0.42 ;95% CI 0.30-0.61; p<0.0001	HR 0.07; 95% CI 0.03-0.14; p<0.0001

3.2 Abiraterone plus prednisone in combination with ADT drug regimen

In several studies of this combination regimen in Japan, participants were randomly assigned to the new regimen--AAP + ADT (Abiraterone acetate 1000 mg + Prednisone 5 mg daily + ADT) or the regular regimen CAB (Bicalutamide 80 mg. daily), the former provides better PFS and OS (progression-free survival and overall survival). Therefore, the investigator gave a medication recommendation, that is, the combination of AAP and ADT in the early stage [8]. However, no clear results have been given on the feasibility of long-term combination medications.

Table2 Comparison of combination therapy

	AAP + ADT	CAB
PFS for 2 years	71.5%	36.1%
2 years of OS	91.3%	80.8%

4 Combination of ADT drugs and chemotherapy drugs

Combination regimens in this category are mainly ADTs in combination with docetaxel (a paclitaxel, most chemotherapy drugs associated with prostate cancer fall into this category). The combination regimen (ADT plus docetaxel 75 mg per square meter of body surface area every 3 weeks for 6 cycles) is primarily for metastatic hormone-sensitive prostate cancer. In the early randomized trials, the median time to prostate cancer progression was 20.2 months compared with 11 months in the ADT group, and the specific antigen levels were much lower than those in the ADT group, and the incidence of associated adverse effects such as neutropenia and neuropathy was also reduced [9]. In addition, such combinations can also improve the growth hormone insulin like growth factor (GH-IGF-1) axis (which is associated with prostate cancer tumorigenesis). Furthermore, there was a significant increase in IGF-1 and its family of

proteins relative to the single ADT group, which plays an important part in the IGF-1 system. At the same time, the researchers found that the combination group had longer OS after statistical (meta-analysis), indicating the advantages of the combination [10].

Table3 The average increase of IGF-1 and its family proteins in each group

	IGF-BP1	IGF-BP3	IGF-BP4
Joint group	Δ+27.4%,p=0.033	Δ+10.3%,p<0.001	Δ+31.1%,p<0.001
Single-medication group		Δ+5.5%,p=0.015	

5 Combination of ADT drugs and immunotherapy

Although most of the combinations of these drugs are in the stage of theoretical and mechanistic research, the latest research is mainly related to pembrolizumab (a PD-L1 inhibitor), and some of them have entered the clinical application stage. In addition, some related combination drug methods are less effective than monotherapy for patients, and even have greater side effects. So, this combination regimen is more developable, but at the same time more expensive and difficult to implement.

5.1 Abiraterone acetate and prednisone in combination with pembrolizumab

The combination regimen: intravenous pembrolizumab 200 mg every 3 weeks for 35 cycles (approximately 2 years), plus oral abiraterone 1000 mg once a day and prednisone 5 mg twice a day. In trials conducted in multiple people and different regions, the PSA response rate in the overall population was only 56% (with a limited reduction from normal abiraterone treatment - 62%), and the combination of the two drugs showed anti-tumor activity, and the tolerability and safety were generally similar to the individual profile of each drug. [11]

6 Discussion

In recent years, the research on ADT drugs has mainly focused on the exploration of new drugs and combination drug regimens, especially new endocrine-related drugs, such as relugoli, abiraterone, enzalutamide, etc. The development of this new drug has compensated for the side effects of some ADT drugs (especially cardiovascular-related side effects) to a certain extent, and at the same time improved the efficacy of the drug (especially for the longer survival of patients and early detection of tumor related proteins).

In addition to the more traditional combination regimens mentioned above, there are also some more novel combination regimens that were provided in recent years, such as ADT in combination with docetaxel and lycopene (a carotenoid found in plant foods), which can reduce the toxic effects of the original drug alone, and at the same time, the pharmacokinetics are better. In addition, Emily Garcia et al. proposed that the combination of reactive oxygen species produced by prostate cancer cells and tyrosine kinase inhibitors sensitize the lysosomal gonadotropic agent siramesine, an approach that can induce ROS-mediated cell death and can be used as an effective treatment method for advanced prostate cancer.

In addition to the combination of ADT drugs with various medications, ADT drugs are also combined with radiotherapy (mainly RT) for treatment. Most of these treatment plans first use RT for fundamental treatment and then ADT drugs for long-term control treatment. This combined treatment approach can improve PFS and OS, but it cannot avoid the side effects of radiotherapy itself, such as bone marrow suppression, skin reactions, gastrointestinal reactions, etc.

Although the cost of combined drugs has increased, it is not completely applicable to all patients, and even some combination drug regimens are harmful and unprofitable. In numerous trials conducted by researchers, it has been confirmed that many combined medication regimens, after being proposed and implemented, have side effects greater than those of single-drug regimens, and their therapeutic effects have not achieved a synergistic effect. However, for some specific groups of people and specific conditions, combination drugs can reduce side effects and improve drug efficacy. So, how to accurately grasp the patient's condition and provide the best medication plan is the most urgent work direction for medical workers at present.

Combination drugs are reshaping the disease treatment landscape through multi-mechanism synergy, reduced toxicity, and expanded indications. In the future, driven by precision medicine and cutting-edge technology, its application will be more intelligent and individualized, but it is still necessary to know the risks in advance, and the relevant clinical applications must also be strictly controlled. Furthermore, it is necessary to consider the cost of the drugs.

Future combination therapy regimens about the prostate cancer should not be limited to traditional combinations. Instead of solely focusing on the further development of multiple combination therapies that include novel endocrine

agents, immunotherapies, and chemotherapeutic agents, it may be more beneficial to seek new combinable drugs and apply these discovered regimens to the treatment of prostate cancer, where current treatment options are limited or associated with significant side effects. A diverse selection of options can provide patients with more personalized treatment plans, thereby alleviating conflicts between physicians and patients while delivering better treatment outcomes.

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