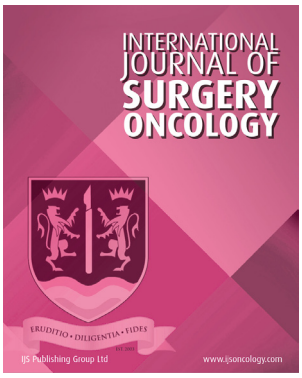

Current Status of Castration-Resistant Prostate Cancer Drug Therapy

REVIEW ARTICLE

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ABSTRACT

Objective: To explore the current therapies on castration-resistant prostate cancer (CRPC), such as drug therapy and radiotherapy.

Recent Advances: Currently, CRPC is an incurable disease. CRPC treatment options available can only relieve symptoms and prolong the survival time. Because of the in-depth study of resistance mechanisms, various new drugs have been reported, including androgen synthetic inhibitor, abiraterone. Novel targeted therapy and immunotherapy have been thoroughly investigated. The recent advances in well-studied radiotherapy and chemotherapy against CRCP have also been reviewed. In this review, we have summarized new generation hormone drugs (e.g., abiraterone, enzalutamid), chemotherapeutic drugs (docetaxel), targeted therapy drugs, immunotherapy drugs (Sipulecel-T), and radioactive drugs (Radium 223). The overall treatment goals include to prolong OS, to improve quality of life, to relieve symptoms, and to prevent complications in CRCP patients.

Conclusions: The use of drug therapy in combination with other drugs might improve the efficacy of CRPC treatment and might help overcome drug resistance.

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1. INTRODUCTION

Prostate cancer is the second most common cancer and the fifth leading cause of male cancer deaths worldwide. According to GLOBOCAN statistics, a total of 1, 276, 106 new cases and 358, 989 deaths occurred in 2018 worldwide [1]. Prostate cancer is the second most common male malignant tumor in the United States [2]. The American Cancer Society estimated 250, 000 new cases and 34, 000 deaths in the United States in 2021 [3]. A statistical study reported about 72, 000 new cases of prostate cancer and 30, 700 deaths in China in 2015 prostate cancer ranked sixth in the incidence spectrum and tenth in the death spectrum of male malignant tumors [4]. In contrast, the incidence and mortality rate in China are slightly lower than the global level; however, an increased tendency has been observed in China in recent years.

In 1941, Huggins *et al.* reported that castration treatment or a large dose of estrogen injection could cause a sharp decrease in acid phosphatase level or decrease it to the normal level [5]. Since then, androgen deprivation therapy (ADT) has been a common therapy for locally advanced or metastatic prostate cancer. However, most patients with metastatic hormone-sensitive prostate cancer developed castration-resistant prostate cancer (CRPC) within 2–3 years after the beginning of ADT treatment, and the patients had low circulating testosterone level [6, 7], The median survival of patients with CRPC was 15–36 months; however, the specific survival rate depended on the disease's severity [8]. European Urology Association defines CRPC as castrated serum testosterone <50 ng/dL or 1.7 nmol/L with biochemical progression (prostate-specific antigen (PSA) successively rises three times in a week, two of which exceed 50% of the lowest point, PSA >2 ng/mL) or radiological progression (bone scans show two or more new bone lesions or Response Evaluation Criteria in Solid Tumors is applied to show soft tissue lesions) [9].

Although CRPC cannot be cured, various drugs can delay disease development and the overall survival (OS) of patients can be prolonged. In this review, we have summarized new generation hormone drugs (e.g., abiraterone, enzalutamid), chemotherapeutic drugs (docetaxel), targeted therapy drugs, immunotherapy drugs (Sipulecel-T), and radioactive drugs (Radium 223) (***Table 1***).

2. NOVEL HORMONE DRUG THERAPY

2.1 ANDROGEN SYNTHETIC INHIBITOR

Abiraterone is an effective inhibitor of cytochrome P450-C17, which is an essential enzyme in androgen synthesis mediated by cholesterol. It can effectively block androgen synthesis in the adrenal gland, testis, and prostate tumors by inhibiting hydroxylase and lyase activities irreversibly [10, 11]. In phase III trials, a total of 1, 199 patients with CRPC were randomly divided into the abiraterone group (ADT + abiraterone + prednison) and the placebo group (ADT + double placebo). The results showed that the median survival time of patients in the abiraterone group was significantly longer than that of patients in the placebo group (hazard ratio of death: 0.62; 95%CI: 0.51~0.76; P < 0.001). The median survival time of radiographic progression-free of patients in the abiraterone group was significantly longer (33.0 months) than that of patients in the placebo group (hazard ratio of disease progression or death: 0.47; 95% CI: 0.39~0.55; P < 0.001). Abiraterone acetate and prednisone significantly increased the overall survival rate and radiographic progression-free survival rate in patients with newly diagnosed, metastatic, castration sensitive prostate cancer [12].

In the SWITCH study, 26 metastatic CRPC (mCRPC) patients with PSA and/or limited radiological progression received abiraterone + dexamethasone (AAD) treatment for at least 12 weeks after AAP treatment. The results showed that PSA30 and PSA50 were 46.2% and 34.6%, respectively. The median time of biochemical and radiological progression was 5.3 and 11.8 months, respectively. The average OS was 20.9 months. These results indicated that steroid conversion was a feasible and safe strategy in the case of abiraterone resistance after its long-term use [13].

2.2 ANDROGEN RECEPTOR (AR) INHIBITOR

2.2.1 Enzalutamid

As a second-generation androgen receptor (AR) inhibitor, enzalutamid can directly bind to the AR to block androgen synthesis, AR nuclear translocation, and DNA binding mediated by androgen. Enzalutamid can be used in the treatment of non-metastatic and metastatic diseases including mCRPC at the beginning of chemotherapy [14, 15]. In a latest study, patients with non-metastatic CRPC (nmCRPC) were randomly divided into the enzalutamid group and the placebo group at a ratio of 2:1. The median OS in the enzalutamid group was 67.0 months (hazard ratio of death: 0.73; 95%CI: 0.61~0.89; P = 0.001). The results indicated that PSA level in patients with nmCRPC increased rapidly, indicating that enzalutamid could prolong the median OS and lower the death risk. [16]

No significant difference was found among PSA progression, clinical or radiological progression, or disease death in a comparative experiment with abiraterone. However, enzalutamid showed a better PSA response and the proportion of patients with PSA reduction ≥50% within 12 weeks was higher than that of abiraterone (75% vs. 54%, $P = 0.004$, Fisher exact test) [17]. In another study combined with AAP, patients in the combined and control groups had similar progression-free survival time. However, grade 3 hypertension (10% vs. 2%) and high alanine aminotransferase (6% vs. 2%) or aspartate aminotransferase(AST) (2% vs. 0%) were more

	AUTHOR (YEAR)	OBJECTIVE (NUMBER)	CONTROL (NUMBER)	METHODS	RESULTS
Androgen synthetic inhibitor					
abiraterone	Fizazi K [12] (2017)	ADT+abiraterone+ prednison (597)	ADT+Double placebo (602)	RCT	the median survival time ↑ (hazard ratio of death: 0.62; 95%CI: 0.51~0.76; P < 0.001). The median survival time of radiographic progression-free ↑ (33.0 months) (hazard ratio of disease progression or death: 0.47; 95% CI: 0.39~0.55; P < 0.001).
Androgen receptor inhibitor					
enzalutamid	Cora N Sternberg [16] (2020)	Enzalutamide (933)	Placebo (468)	RCT	Median OS ↑ (67.0 months vs 56.3 months)(hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89; P = 0.001). The risk of death associated with enzalutamide was 27% lower than with placebo. Adverse events were consistent with the established safety profile of enzalutamide.
apalutamide	Matthew R Smith [21] (2018)	Apalutamide (806)	Placebo (401)	RCT	median metastasis-free survival ↑ (40.5 months vs 16.2 months) i (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P < 0.001).Time to symptomatic progression ↑ (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; P < 0.001).
darolutamide	Fizazi K [25] (2020)	Darolutamide (955)	Placebo(554)	RCT	Overall survival at 3 years ↑ (83% vs77%). The risk of death ↓, by 31% (hazard ratio for death, 0.69; 95% CI, 0.53 to 0.88; P = 0.003).
Chemotherapeutic drugs					
Docetaxel	Daniel P Petrylak [32] (2004)	Docetaxel+ Estramustine (336)	Mitoxantrone+ Prednisone (338)	RCT	The median overall survival ↑ (17.5 months vs. 15.6 months, P = 0.02 by the log-rank test), the corresponding hazard ratio for death was 0.80 (95 percent confidence interval, 0.67 to 0.97). The median time to progression ↑ (6.3 months VS 3.2 months).
Cabazitaxel	Ronald de Wit [38] (2019)	cabazitaxel (129)	androgen-targeted inhibitor (126)	RCT	imaging-based progression or death ↓ (73.6%vs80.2%) (hazard ratio, 0.54; 95% confidence interval [CI], 0.40 to 0.73; P < 0.001). The median imaging-based progression-free survival ↑(8.0 months vs 13.6 months) (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.89; P = 0.008). The median progression-free survival ↑ (4.4 months vs 2.7 months) (hazard ratio for progression or death, 0.52; 95% CI, 0.40 to 0.68; P < 0.001).

Table 1 Current status of castration-resistant prostate cancer drug therapy.

ADTandrogen deprivation therapy RCTrandomized controlled trial ↑: increase; ↓: reduce.

frequent in the combined group than those in the control group. These results indicated that during enzalutamid treatment, a higher rate of side effects was observed when it was combined with enzalutamid, abiraterone, and prednisone [18].

2.2.2 Apalutamide

Apalutamide is a high-affinity AR inhibitor and can prevent AR nuclear translocation [19, 20]. In phase III trial, a total of 1, 201 patients with nmCRPC were randomly divided into the apalutamide group and placebo group at a ratio of 2:1. The results demonstrated that the median metastasis-free survival time in the apalutamide group extended by 24.3 months (hazard ratio of metastasis or death: 0.28; 95%CI: 0.23~0.35; P < 0.001) and the time to symptomatic progression was significantly longer than that in the placebo group (hazard ratio: 0.45; 95%CI: 0.32~0.63; P < 0.001). The results demonstrated that apalutamide had a significant clinical response in patients with nmCRPC [21].

A total of 1171 SPARTAN patients were matched with 1, 401 PROSPER patients. Based on the matching-adjusted indirect comparison method, we found that the incidence of fatigue [p (OR <1) = 99.5%], hypertension [p (OR <1) = 99.2%], headache [p (OR <1) = 86.7%], nausea [P (or <1) = 80.0%], and loss of appetite [p (OR <1) = 98.3%] in the apalutamide group was significantly lower than that in the enzalutamid group. Apalutamide treatment decreased the incidence of adverse events and serious adverse events by 66.9% and 90.9%, respectively, patients administered with apalutamide had a higher tolerance toward nmCRCP treatment [22]. However, patients who received apalutamide were more likely to develop multiple sclerosis and osteoarthritis than those who received enzalutamid [23].

2.2.3 Darolutamide

Darolutamide is an androgen inhibitor with a unique structure, and has been approved for nmCRPC treatment [24]. In the latest research, a total of 1, 509 males were randomly divided into the darolutamide group (955 patients) and placebo group (554 patients). The results showed that the 3-year survival rate was 83% in the darolutamide group (95%CI: 80~86) and 77% in the placebo group (95%CI: 72~81). The risk of death reduced to 31% (hazard ratio of death: 0.69; 95%CI: 0.53~0.88; P = 0.003). These results indicated that the metastasis-free survival time and OS of patients with nmCRPC were significantly prolonged after darolutamide treatment without changing the rate of adverse reactions [25].

Darolutamide can inhibit the growth of enzalutamid-resistant MR49F cells and AR transcription activity in vitro. Moreover, darolutamide also significantly inhibited the transcriptional activity of the mutant, which could convert enzalutamid into a partial agonist, such as F877L, H875Y/T878A, and F877L/T878A. Darolutamide can be used to delay the growth of enzalutamid-resistant prostate cancer [26].

The direct comparative data on nmCRPC treatment with new generation AR inhibitor is lacking, and is present only in the form of network meta-analysis. Apalutamide has been the best choice for metastasis-free survival(MFS) (P = 0.8809). Apalutamide has been the leading scheme for PSA-benign prostatic hyperplasia syndrome (P = 1.000). Darolutamide has been the best choice for adverse events (e.g., grade 3 or 4 adverse events, grade 5 adverse events, and drug withdrawal rate). Apalutamide and enzalutamid are effective drugs for nmCRPC treatment, whereas darolutamide has the most favorable tolerance [27].

3. CHEMOTHERAPEUTIC DRUGS

Mitoxantrone was approved by the Food and Drug Administration (FDA) for mCRPC treatment in 1996. In two clinical trials (in 1996 and 2002), mitoxantrone did not affect the survival rate of patients [28, 29]. SUN 1120 and TERIC data analysis showed that the median survival time of patients treated with mitoxantrone + prednisone was similar to that of patients treated with prednison only (385 days vs. 336 days; deceleration factor = 0.04; 95% CI: −0.12 to 0.22). Research showed that mitoxantrone had no considerable survival benefit after docetaxel treatment [30], and was gradually replaced by docetaxel and cabazitaxel.

Docetaxel can induce apoptosis by inhibiting microtubule depolymerization and by blocking anti-apoptotic signal, and can be used as the first-line drug for mCRPC treatment. The TAX327 test and the Southwest Oncology Group (SWOG) 99–16 test confirmed that docetaxel could improve the median OS of mCRPC patients (1.9–2.4 months) [31–33].

A total of 98 CRPC patients, including 46 nmCRPC patients and 52 nmCRPC patients who received docetaxel treatment were analyzed in a trial. OS of patients in the nmCRPC group was significantly longer than that of patients in the mCRPC group (not reached vs. 52.2 months, P = 0.006). For patients with nmCRPC, the early induction of docetaxel might have prolonged OS [34].

Cabazitaxel leads to cell death via tubulin stabilization, and can be used to overcome docetaxel resistance mediated by multidrug resistance protein (P-glycoprotein). Cabazitaxel has been approved to treat mCRPC patients that were previously treated with docetaxel but developed docetaxel resistance [35–37]. A total of 255 mCRPC patients who had previously received docetaxel and androgen-targeted inhibitor were randomly divided into the cabazitaxel group (129 patients) and androgen-targeted inhibitor group (126 patients) at a ratio of 1:1. In the cabazitaxel group, the median of progression-free survival time based on the

radiography extended by 4.3 months, the median OS prolonged by 2.6 months (hazard ratio of death: 0.64; 95%CI: 0.46 to 0.89; P = 0.008), and the median of progression-free survival time extended by 1.7 months (hazard ratio of progression or death: 0.52; 95% CI: 0.40 to 0.68; P < 0.001). Studies have shown that cabazitaxel considerably improved the clinical outcomes in patients with mCRPC who had previously received docetaxel or AR-targeted inhibitor [38].

4. TARGETED DRUGS

Poly(adenosine diphosphate–ribose) polymerase (PARP) is a ribozyme that plays an essential role in cell repair mediated by deoxynucleotide. Tumor cells with BRCA1/2 or Ataxia telangiectasia mutated (ATM) deficiency require DNA repair mediated by PAPR. Studies have shown that about 20% of patients with mCRPC had significant mutations in BRCA1/2 or ATM [39–41].

Olaparib is a PARP inhibitor and has been approved by the FDA for the treatment of BRCA1/2 or ATM mutant CRPC in January 2016 with approximately 90% of effective rate [42]. In phase III trial, 245 mCRPC patients with new hormone drug resistance who had at least one change in BRCA1, BRCA2, and ATM were divided into the olaparib group and the control group at a ratio of 2:1. The results showed that radiographic progression-free survival time in the olaparib group was significantly extended (7.4 m vs. 3.6 m; hazard ratio of progression or death: 0.34; 95% CI: 0.25 to 0.47; p < 0.001) and anemia and nausea were the main toxic reactions [43].

Treatment of mCRPC by another PARP inhibitor, rucaparib, requires further study [44]. In TRITON2 trial, 115 mCRPC patients (BRCA1/BRCA2 change) administered with AR inhibitors and chemotherapeutic drugs were treated with 600 mg rucaparib twice a day.

The results showed that the risk rate of radiology examination was 43.5% (95%CI: 31.0% to 56.7%; 27 out of 62 patients), the response rate of PSA was 54.8% (95%CI: 45.2% to 64.1%; 63 out of 115 patients) and the most common treatment-emergent adverse event ≥ grade 3 was anemia (25.2%; 29 out of 115 patients). Rucaparib treatment showed changes in anti-tumor activity against breast cancer in mCRPC patients; however, breast cancer has the same manageable safety as other solid tumor types [45].

5. IMMUNOTHERAPY

Sipulecel-T is the only immunotherapeutic drug approved by the FDA, and is used to treat asymptomatic or minimum symptomatic mCRPC. The activation of antigen-presenting cells can induce strong and long-lasting antigen-specific humoral and T cell reactions and T cells transport to tumor tissue, which stimulates local and systemic cytotoxic T lymphocyte activity and promotes antigen diffusion. Based on IMPACT trial, the median OS of patients was prolonged by 3.4 months [46, 47].

A total of 3216 patients administered with sipuleucel-T from 2010 to 2017 had the most common adverse reactions including shivering (n = 318), discomfort (n = 196), fever (n = 189), fatigue (n = 180), and nausea (n = 173) [48]. In one trial, 18 patients with mCRPC were divided into two groups; one group received intradermal injection with Sipuleucel-T and another received pTVG-HP DNA vaccine alone. A high titer of PAP antibody was detected in patients receiving supplementary pTVG-HP vaccine. These results indicated that the initial supplementary vaccination could enhance and diversify the immune responses induced by anti-tumor vaccine. Further studies on DNA vaccines as an immune promoter need to be performed. [49]

Programmed cell death protein-1 and its ligands, programmed death-ligand (PD-L)1 and PD-L2, transmit signals that inhibit T cell activation [50, 51]. Pembrolizumab has anti-tumor activity against positive mCRPC. KENNNETH-199 research showed that patients with bone-based mCRPC had acceptable safety with the disease control rate of 22% and the median OS of 14.1 months [52]. PD-L1 is associated with poor prognosis and advanced clinicopathological factors of prostate cancer. The analysis of 3, 133 patients before March 23, 2020 showed that PD-L1 protein expression and PD-L1 DNA methylation were negatively correlated with the biochemical recurrence-free survival rate, and their hazard ratios (HRs) were 1.67 (95%CI = 1.38 to 2.06, P < 0.001) and 2.23 (95%CI = 1.51 to 3.29, P < 0.001), respectively. PD-L1 overexpression was significantly correlated with advanced prostate cancer (OR = 1.40, 95%CI = 1.13 to 1.75, p = 0.003) and positive AR (OR = 2.20, 95%CI = 1.61 to 3.01, *P* < 0.001). PD-L1 was associated with poor prognosis and advanced clinicopathological factors of prostate cancer [53].

6. RADIOACTIVE DRUGS

6.1 RADIUM 223

Radium 223 is an -particle emitter and calcium mimic, which targets the hydroxyapatite matrix in the bone. Radium 223 accumulates in the areas of active bone remodeling and formation, such as the site of osteoblast bone metastasis. Radium 223 was administered to CRPC patients with bone metastasis symptoms without visceral metastasis, and it improved OS rate. [54, 55] In phase III trial, Radium 223 was administered to 708 patients with mCRPC, among which 548 had various symptoms and 135 had no symptoms. The results showed that the OS (hazard ratio [HR] 0.486), the time of disease progression (HR 0.722), the time of the first bone event

with a symptom (HR 0.328) in asymptomatic patients were better than those in symptomatic patients, and the PSA response rate was also higher in the asymptomatic patients (21% vs. 13%). These results indicated that radium 223 could be considered a complete treatment option for asymptomatic CRPC patients or patients with mild symptoms [56]. In a latest trial, the supplementation of radium 223 in the AAP regimen did not improve the survival rate of CRPC patients with bone metastases, and the frequency of fracture increased. Therefore, radium 223 in combination with AAP is not recommended [57, 58].

6.2 RADIOTHERAPY

Prostate-specific membrane antigen (PSMA) is expressed on the cell membrane of prostate epithelial cells and is considerably upregulated in prostate cancer. PSMA is an appropriate target for diagnosing, treating, and determining the metastasis of prostate cancer [59, 60]

177Lu-PSMA-617 is a potential new radioligand therapy for mCRPC, and capable of targeted delivery of -particle radiation to prostate cancer [61–63]. The results showed that about 2/3 of PSA and 1/3 of PSA was decreased by more than 50%, and the survival period was prolonged after the first week of radiotherapy [64]. In phase II prospective trial, 50 patients (short median time of PSA multiplication and extensive previous treatment) received 177Lu-PSMA-617 with an average radiation dose of 7.5 GBq/period for 4 cycles. A total of 22 patients (44%; 95%CI: 30% to 59%) had at least 50% of specific antigen reduction and 22 patients (44%; 95%CI: 30% to 59%) had 80% of specific antigen reduction. With a median follow-up time of 31.4 months, median OS was 13.3 months (95%CI: 10.5 to 18.7 months) and the survival time of patients with PSA decreased by at least 50% was significantly prolonged to 18.4 months (95%CI: 13.8 to 23.8 months). The main adverse reactions were mouth dryness (66%), transient nausea (48%), thrombocytopenia (10%), and anemia (10%). These results indicated that 177Lu-PSMA-617 had a high response rate and low toxicity, and improved life quality [65].

7. OUTLOOK

CRPC is still an incurable disease. Currently, the main treatment goals are to prolong OS, improve quality of life, relieve symptoms, and prevent complications. Various drugs and their combinations have been reviewed to identify whether they can improve the curative effect and prevent drug resistance. The opening of new generation androgen drugs has dramatically improved the OS of CRPC patients; however, more research is needed on immunological drugs.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Yifeng Mao contributions: data collection, drafting and critical revision of the manuscript. Mingqiu Hu contributions: drafting and critical revision of the manuscript.

Gaowei Yang, Erke Gao and Wenbang Chen contributions: study design and conception, drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

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