Homologous Recombination Deficiency and Prostate Cancer

Subjects: Oncology | Urology & Nephrology

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Homologous recombination deficiency (HRD) is a term describing tumor phenotypes in which the ability to repair DNA double-strand breaks utilizing the homologous recombination repair (HRR) pathway is lost. Lately, precision medicine has been focusing on targetable mutations, although their frequency in tumors may be very low. The most notable mutations that can be targeted in PCa include gene products that regulate DNA repair through homologous recombination (HR), such as BRCA1, BRCA2, ATM, PALB2, CHEK2 and HOXB13.

prostate cancer | DNA damage repair | homologous recombination deficiency | biomarkers

1. Introduction

Homologous recombination repair (HRR) is part of the DNA damage repair (DDR) pathway that also includes base excision repair, nucleotide excision repair, mismatch repair and non-homologous end joining [1][2]. HRR is activated during the S and G2 phases of the cell cycle and is a very efficient and error-free process, in contrast to non-homologous end joining, which repairs errors at any phase of the cell cycle and has a propensity for errors [1]. The importance of such mechanisms is substantial, as it defines the fate of the cell after DNA damage [3]. After exposure to carcinogens, including endogenous or exogenous factors such as ultraviolet and ionizing radiation and chemical pollutants that cause oxidative stress, DNA damage repair (DDR) is activated before the cell commences replication [3][4]. DDR recruits tumor suppressor proteins and restrains the aggregation of genomic alterations [2]. If the damage is extensive, then cell death occurs, since the accumulation of double- and single-strand breaks may lead to genomic instability, which carries a risk of malignant transformation [3][4][5].

DNA repair enzymes are found mutated in a variable proportion of prostate cancer (PCa) cases, ranging from 5–10% in localized disease to almost 20% in advanced, castrate-resistant or metastatic disease [1][2][3][6][7][8][9][10]. Analysis of 333 cases of primary PCa retrieved from The Cancer Genome Atlas (TCGA) demonstrated that mutations in HR genes were detected in 19% of the samples, being present even at the early stages of the disease [4][11]. The most common alterations in the TCGA database were ATM mutations (4%), RAD51C deletions (3%), BRCA2 deletions or mutations (3%), CKD12 deletions or mutations (2%), BRCA1 mutations (1%) and FANCD2 aberrations (6%) [4]. In a study including 150 patients with recurrent or metastatic PCa, without any further selection, 14% of the patients were found to harbor pathogenic mutations for enzymes that mediated DNA damage repair in their tumors and BRCA2 was the most commonly affected gene [10][12]. HRD gene aberrations are considered an early-stage event in PCa, but their more frequent occurrence in advanced disease is explained by their association with a poor prognosis [13] and their role in disease progression [2].

2. Germline vs. Sporadic Mutations in Homologous Recombination Genes

Alterations in HR genes are most commonly sporadic but can also be germline [14]. The term *inherited PCa* refers to families that fulfill the John Hopkins criteria, these being the following: (a) at least three first-degree relatives diagnosed with PCa, (b) the presence of the disease in three consecutive generations and (c) early-onset disease in two family members [15].

It is well established that a family history of PCa increases the risk for all male relatives, even in the absence of characteristic genetic alterations [16][17]. These cases, comprising 15–20% of all patients, are best described with the term “family-associated PCa” and should not be confused with hereditary PCa, which occurs less frequently, at an estimated 5% [17], and includes a population with a specific molecular profile—for instance, *BRCA1/2* or *HOXB13* mutation carriers [16]. A proposed theory is that the predisposition in families with a higher incidence of PCa probably occurs due to the interplay between common polymorphisms of intermediate and low penetrance in various genes with environmental risk factors that enhance inflammation [17].

A hereditary predisposition to PCa should be suspected when there is a family member diagnosed with PCa at an age < 60 years or with an aggressive disease course, a family history of more than three malignancies related to hereditary breast/ovarian cancer or Lynch syndrome or, finally, in men of Ashkenazi Jewish origin [18] and if two distinct histological patterns are seen in a prostate biopsy: intraductal carcinoma of the prostate (IDCp) and cribriform histology (see below) [12][16][19][20].

The PRACTICAL study analyzed germline mutations in men predisposed to PCa and demonstrated that mutations that are considered pathogenic or likely pathogenic in genome databases (for instance, ClinVar) were linked with a worse prognosis, a fact that was not observed for mutations classified as variants of uncertain significance. This means that the detection of a mutation or variant alone is not informative, and further characterization of the genetic alteration detected is required in order to obtain accurate predictive information for the patient [21].

Germline mutations in DDR have distinct behavior and malignant potential compared with sporadic cases [4]. Somatic mutations can develop after progression to metastatic CRPC (mCRPC) [8], while germline mutations are inherited through an autosomal dominant pathway with incomplete penetrance [1]. Germline *BRCA2* mutations have especially been associated with a poor prognosis and have been found to be an independent prognostic factor for PCa patients [22][23], and this applies even in cases with a limited tumor volume and low histopathological grade [8]. These neoplasms demonstrate higher genomic instability and more copy number alterations [8], including *MYC* amplification, which is known to correlate with aggressive behavior and rapid disease progression [24]. The aggressiveness of *BRCA2*-mutated neoplasms has been attributed to the fact that these tumors develop a subpopulation of cells that are castrate-resistant and can grow independently, even after the administration of antiandrogen therapy. This model is supported by research data that show a similar molecular signature in *BRCA2*-mutated tumors and metastatic CRPC, which is only rarely found in sporadic PCa [8]. Another theory is that these neoplasms, due to the DNA repair defects that they harbor, gradually accumulate genetic alterations, in contrast to

sporadic cases with functionable DNA repair systems, where DNA defects are properly and timely repaired [8]. It has been proposed that genetic alterations, characterized as truncal, arise at the early stages of carcinogenesis and are carried by all the daughter cells, while later-acquired alterations are present only in specific cell subpopulations, contributing to the heterogeneity and complexity of cancer genetics [16].

The presence of germline mutations has additional implications for the relatives of the patient, as they should be tested as potential carriers [6][7][16]. Of interest, 5.5% of men with a familial predisposition to PCa share the same mutational pattern in DNA repair enzymes, such as *BRCA1*, *BRCA2* and *ATM* alterations, even if they have not developed PCa [6]. Experts suggest to start screening for PCa in men with known *BRCA2* and *BRCA1* mutations at the age of 40 [7], supported by studies that have revealed a diagnosis of PCa at as early as 41 years of age in *BRCA2*- and 43 in *BRCA1*-mutated patients [25].

3. BRCA and Non-BRCA Mutations

BRCA mutations represent the most common DNA repair alterations in PCa [1] and, among them, the majority of cases show *BRCA2* alterations (12% *BRCA2* alterations versus 2% *BRCA1* in advanced PCa) [2][4][13][16]. The most common *BRCA2* alteration results in the production of a truncated form of the protein, followed by complete deletion of the gene; only a minority of cases show point mutations [16]. In contrast, the most frequent *BRCA1* mutations lead to a truncated gene product and are often accompanied by *TP53* mutations [26].

HOXB13 was the first gene that was shown to enhance the prostate cancer risk by up to 10 times and was linked with familial cases of PCa and early-onset disease in some [7][15][17] but not all studies [27]. Specifically, the mutant HOXB13G84E has been associated with lower-risk tumor characteristics [27], early-onset disease [17] and European origin among patients [15][17]. Other alterations have been encountered in different populations, such as G135E in Chinese men and variants A128D and F240L in Portuguese men [15].

A recent study conducting genome analysis on non-BRCA-mutated PCa showed that germline *ATM* and *CHEK2* alterations had lower penetrance than *BRCA2*. In addition, prostate cancer carried different genetic alterations in these genes compared to breast and ovarian cancer [27]. Germline *CHEK2* mutations increase the risk for PCa development at a moderate level [7] and have been linked with aggressive or high-risk cancer [27]. Genome analysis in patients with non-*BRCA*-mutated familial PCa has confirmed that mutated *ATM* is found in cases with advanced disease, higher PSA levels at the time of initial diagnosis and a high D'Amico score [27]. Further studies need to be performed, mainly for *ATM* and *PALB2*, as the existing data for these two genes in PCa are limited. It is promising, though, that *ATM* aberration augments the sensitivity to PARP inhibitors [28].

CDK12 is a cyclin-dependent kinase that regulates transcription elongation through the phosphorylation of RNA polymerase II, subsequently modifying gene expression and influencing DDR gene expression [29]. *CDK12* is mutated in a small percentage of metastatic castrate-resistant PCa (CRPC), varying from 4.7% to 7%, and, when mutated, it is not combined with HR deficiency and *ATM* or MMR gene mutations [30][31]. Thus, *CDK12*-mutant PCa comprises a distinct molecular group of PCa.

4. Clinical and Histologic Characteristics of Homologous Recombination Deficiency Tumors

BRCA2-mutated tumors tend to develop in younger patients, are usually classified as an intermediate or high risk of recurrence, metastasize earlier and are associated with shorter survival, even when treated with prostatectomy or radiotherapy [2][7][8][11][20][25][32][33]. In addition, HRD-targeted therapies have been developed (see below). Thus, tumor testing for HR genes is recommended in all metastatic PCa patients and can be considered in patients with regional disease, especially those with adverse characteristics [34].

The IMPACT study focused on screening men having *BRCA1* and *BRCA2* mutations for the diagnosis of PCa and revealed that the value of prostate-specific antigen (PSA) levels higher than 3.0 ng/mL and of prostate biopsy was greater in the *BRCA2*-mutated population than in the *BRCA2* wild type [25]. In contrast to these data, there are increasing data available showing that PCa with low PSA values at the time of diagnosis is associated with DDR mutations [12], and, in comparison, metastatic cases with a known *BRCA2* [35] but not *BRCA1* [25] mutation present with lower PSA levels compared to their wild-type controls. Another study that tried to elucidate the pathological characteristics of *BRCA2*-mutated tumors exhibited no statistically significant difference compared to *BRCA2* wild-type tumors regarding the TNM classification, prognostic grade group or histology subtype of the tumors [35]. The mutated subgroup, however, had a higher mutational load and recurring *ATM* and *BRCA1* alterations [35].

Intraductal carcinoma, which is associated with high-grade and high-stage PCa; the presence of lymph node and distant metastases; and shorter disease-specific and overall survival is more frequently seen in cases of hereditary PCa and often harbors *BRCA1/2* mutations [20][36][37][38][39][40]. Additionally, *BRCA2* mutation carriers have a higher probability of showing IDCp in their biopsy [8][20][36][41][42][43][44]. Even IDCp associated with low-grade PCa has been shown to harbor aberrations in DDR genes, such as *BRCA2*, *CHEK2* and *CDK12*, which are not present in the invasive component [45]. Furthermore, according to recent data, in PCa without IDCp, HRD (estimated by a higher HRD score—see below) results from mutations in DDR genes, in contrast to PCa with IDCp, where HRD is attributed to *TP53* mutations [46]. Whole-genome sequencing of *BRCA2*-mutated and IDCp-harboring PCa revealed the molecular resemblance of these tumors to metastatic CRPC, even at the initial stages of tumorigenesis, and the activation of crucial signaling pathways, such as WNT/b-catenin modulator MED12L/MED12, which have been associated with an adverse prognosis [20][47]. It should be mentioned that these alterations are not found in sporadic cancers with IDCp, while MED12 is absent in normal prostate and organ-confined PCa [20].

Apart from intraductal carcinoma, the somatic loss of both alleles of the *BRCA2* gene and increased genomic instability and copy number alterations have also been associated with the cribriform pattern and the ductal type of adenocarcinoma [19][44][47][48].

Based on these data, current guidelines suggest that patients with intermediate-risk PCa and IDCp or cribriform histology can be considered for germline or somatic genetic testing for DDR alterations [49][50][51][52][53][54][55][56].

5. Clinical and Therapeutic Implications of Homologous Recombination Deficiency

Based on the aggressiveness of HRD-mutated neoplasms, an earlier and more aggressive therapeutic approach should be followed for *BRCA2*-mutated tumors. Moreover, patients with this molecular signature demonstrate a significant response to platinum-based chemotherapy and poly-adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitors (PARPi) (see below). Regarding platinum-based chemotherapy, HRD has been associated with an increased likelihood of a PSA response in a small cohort (N = 64) of patients with PCa, although no difference in overall survival was seen [57]. However, the number of patients enrolled in this cohort was limited, so these observations need to be validated in larger groups of patients [57][58]. Similarly, a small prospective cohort study showed that patients with germline mutations in DDR experienced better outcomes when treated with abiraterone or enzalutamide, compared to taxanes [22]. In addition, radical prostatectomy, rather than radiotherapy, should be the treatment of choice for these patients in the localized setting [8]. Interestingly, these worrisome features are not detected in *BRCA1* carriers, indicating that the clinical implications of these two mutations are significantly different [25].

Patients with CRPC and HRD alterations show promising response rates after treatment with PARP inhibitors [28]. Therefore, in 2016, PARP inhibitors received approval by the Food and Drug Administration (FDA) and were incorporated into the therapeutic schemes of metastatic CRPC [28]. To date, two PARP inhibitors (Olaparib and Rucaparib) have been approved for metastatic CRPC [59][60]. Clinical data support their efficacy, as documented by PSA and circulating tumor cell responses and improved progression-free survival and overall survival [60].

One of the first clinical trials that elucidated their utility was the TOPAPR-A trial [61]. The patient group included fifty (50) patients harboring alterations in DNA repair enzymes, previously treated with docetaxel or second-generation androgen deprivation therapy (ADT); treatment with Olaparib resulted in a favorable clinical response [61]. Based on the subsequent PROfound clinical trial (NCT02987543) [62] (a randomized phase 3 clinical trial in 245 patients with a mutation in at least one of *BRCA1*, *BRCA2* and *ATM* and 152 patients with alterations in other HRD genes), Olaparib was approved for patients whose tumors harbor a genetic alteration in *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L* as a second-line therapy after the failure of second-generation antiandrogen agents or docetaxel or as a third-line therapy [7]. Based on the Triton 2 (NCT02952534) and Triton 3 (NCT02975934) clinical trials [63][64], Rucaparib has been approved for tumors harboring *BRCA1/2* mutations, either somatic or germline [65][66]. Currently, ongoing clinical trials are tested the efficiency of other members of the PARP inhibitor family, such as niraparib (clinical trial number: NCT02854436) [7].

Proper risk assessment of patients at the time of the initial diagnosis should incorporate the HRD status [46]. Interestingly, different alterations in the genes have recently been found to result in different response rates to treatment [67]. For instance, a PCa patient with a base substitution (c.4211C > G) in *BRCA2* showed a response to radiotherapy and androgen deprivation therapy (ADT) in a Chinese cohort study [68], while patients with CDK12 mutations did not respond well to hormonal therapy, PARPi or taxanes but showed positive (and occasionally

durable) responses to PD-1 inhibition [69][70]. On the contrary, ATM and CDK12 mutations do not seem to respond to PARP inhibitors as effectively as BRCA1/2 mutations [71][72]. Despite the fact that this observation was noticed in a small group of patients (46 patients) with progressive metastatic CRPC, and the retrospective nature of the study, it is in accordance with the results of the Triton 3 trial [71]. A possible reason for this difference is that biallelic loss and germline mutations, which are usually detected in BRCA1/2 carriers, respond better to the treatment [71]. This underlines the importance of accurate sequencing in HR genes in order to be fully utilized as both prognostic and predictive biomarkers.

6. Predictive Biomarkers to Poly-Adenosine Diphosphate Ribose Polymerase Inhibitors Response

Next-generation sequencing (NGS) seems to be the most appropriate tool to detect alterations in the HRD-associated genes mentioned above. This method detects multiple genetic alterations, including mutations and chromosomal alterations in a single test, although none of the currently available tests is validated to detect germline mutations. Genomic analysis with a high reading depth can raise the awareness of hereditary PCa, and these cases should be referred to genetic counseling that provides an holistic approach and guides the patients through specialized genetic tests [16]. NGS testing can be performed on metastatic tissue or on plasma circulating free DNA (cfDNA) [16]. Patients with mutations in genes other than BRCA1/2, such as *ATM*, *PALB2*, *CHEK2*, *FANCA* and *HDAC2*, are also responding well to PARP inhibitors, underlying the importance of using a broader detection panel [28].

A scoring system, called the Homologous Recombination Deficiency Score, has also been established, incorporating several chromosomal aberrations, such as the loss of heterozygosity, telomeric allelic imbalance and large-scale transitions [46]. This score gives, however, a general expression of the HRD status and does not directly reflect which particular enzyme is damaged. Nonetheless, it appears that it can be successfully utilized as a predictive biomarker for the potential response to PARP inhibitors [46]. The presence of *MYC* and *TP53* alterations is also frequently associated with high HRD scores, even without synchronous aberrations in the HR system [46]. The *MYC* oncogene supervises the repair of double-strand DNA breaks [46]. Subsequently, the concurrent inhibition of the MYC pathway along with PARP inhibitors could be beneficial [46].

Regarding the follow-up of patients under PARP inhibitor treatment, a relatively new but promising approach is the whole-exome sequencing of liquid biopsy specimens, which reduces the need for additional surgical interventions in patients [11][58][73][74]. Testing of metastatic tissue poses some practical difficulties, as metastatic foci in PCa are mostly found in the bones, which sometimes are difficult to access; even when the sample is adequate, the DNA that is extracted from this tissue has questionable quality, due to the decalcification that is performed during tissue processing [75].

One of the first applications of liquid biopsy in PCa research was conducted in the TOPAPR-A clinical trial, where it was depicted that cfDNA analysis can provide adequate information regarding acquired genetic alterations, even before signs of clinical progression are evident, allowing the early detection of resistance [2]. The broad utility of this

approach may lead to modifications of the therapeutic scheme and the discontinuation of non-responsive drugs, avoiding unnecessary toxicity [73]. cfDNA is derived from the circulated tumor DNA and DNA fragments that are produced after cellular death or apoptosis [74]. The main disadvantage of this revolutionary method is the small number of circulating tumor cells in some cases, and, thus, the practical difficulty to isolate and further process them in order to extract DNA [58]. Therefore, liquid biopsy is preferably utilized in advanced PCa cases and not in the early stages of the disease.

7. Poly-Adenosine Diphosphate Ribose Polymerase Inhibitors Mechanism of Action

The mechanism of action of PARP inhibitors in HRD tumors has been clarified during the last decade [76]. Normally, the PARP complex consists of 16 enzymes and their common feature is the production of poly(ADP-ribose) from NAD, a chemical reaction that generates nicotinamide [76]. Some members of the PARP family, PARP1 and -2, activate the repair mechanisms after DNA damage [59]. In particular, PARP1 can restore double- and single-strand breaks in the nucleotide chain [59], preserving the integrity of the replication fork and, subsequently, of transcription, thus shielding the genome against replication stress [76]. If this process fails, then replication is interrupted, and deadly breaks, followed by cellular death, are induced [76]. Homologous recombination undertakes the correction of double-strand breaks by enlisting various repair enzymes, including BRCA1 and BRAC2 [76]. PARP1 has a central role in the recruitment of other family members, as the absence of PARP1 downgrades the efficacy of PARP inhibitors in general [76] (**Figure 1**). Furthermore, in experimental models, PARP1 enhances the oncogenic actions of TMPRSS-ERG, through the enrichment of AR-mediated transcription, which eventually drives the cells into a castrate-resistant phase [2]. PARP1 is essential for the activation of ERG [2].

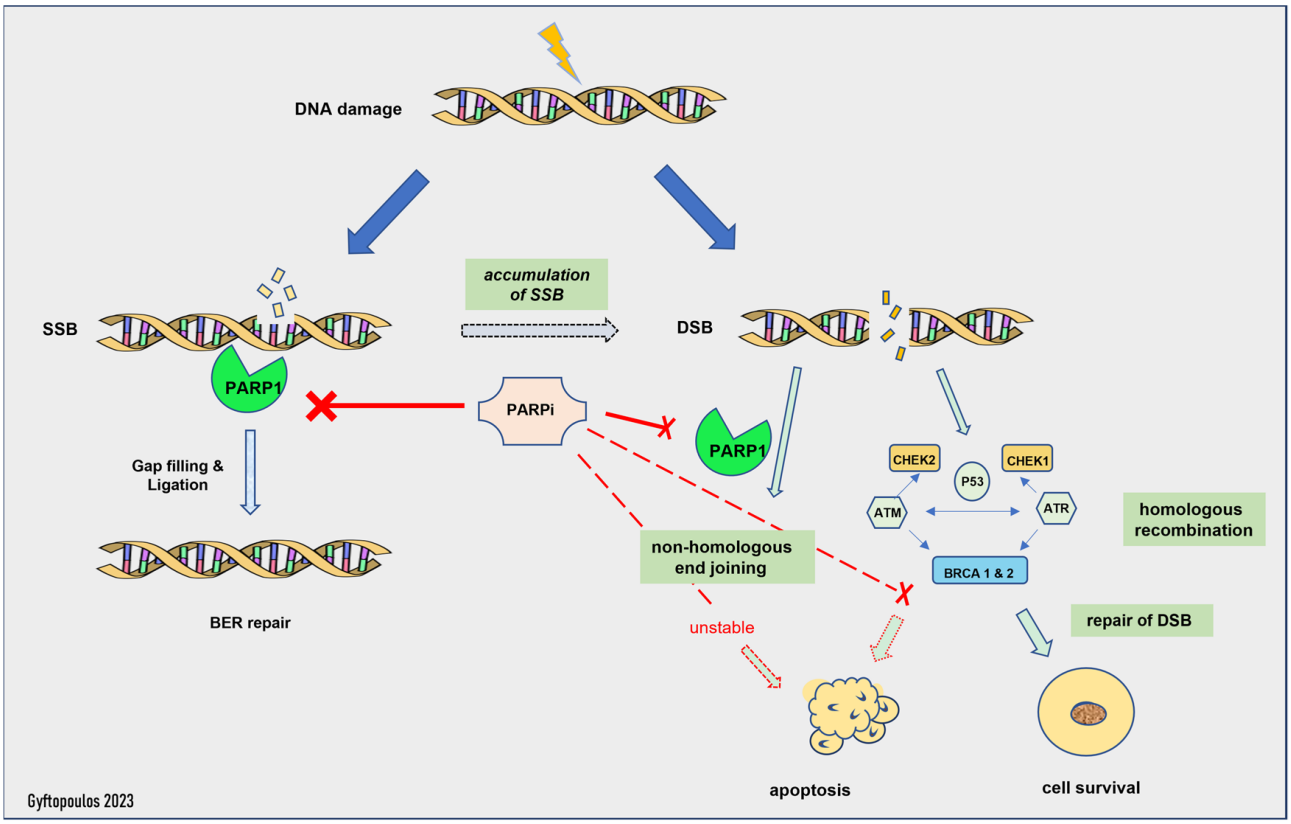

Figure 1. Mechanism of action of PARP inhibitors. SSB: single-strand break, DSB: double-strand break, BER: base excision repair.

The activity of PARP inhibitors is described as PARP trapping, as it traps PARP1/2 near the region of DNA damage, resulting in the stalling of replication forks. Stalled replication forks lead to highly cytotoxic double-strand breaks that, in HR-proficient cells, are repaired by HR [3][60]. HRD cells are unable to repair the accumulating double-strand breaks and die [6]. Thus, PARP1i is effective only in HRD cells, as the HR-proficient cells can escape its action. This is called the synthetic lethality hypothesis [77]. Synthetic lethality describes a situation where a combination of two events leads to cell death, but each event is individually viable. Olaparib inhibits PARP1 and -2, while Rucaparib is a less selective PARP inhibitor with a broader range of action, including non-PARP targets [76]. Of note, patients with germline mutations in the *BRCA* genes suffer from severe adverse effects and especially myelotoxicity [3], whereas most patients with sporadic HRD face milder toxicity, such as anemia and fatigue [61].

Therapeutic synthetic lethality can also be applied to tumors that have a molecular signature similar to *BRCA*-mutated tumors, even in the absence of homologous recombination deficiency, introducing a new term of “BRCAness”. For example, PARP inhibitors have been shown to induce replication stress in experimental models that exhibit the concurrent loss of *P53* and *RB1* and *MYC* amplification [1][76]. This could explain the favorable response to these drugs, even in the absence of *BRCA* mutations [28]. However, despite this experimental evidence, the MAGNITUDE trial failed to show a survival benefit in men who did not harbor HRR mutations and were treated with PARPi (niraparib) combined with abiraterone [72]. On the other hand, platinum-based chemotherapy, such as docetaxel and cabazitaxel, acts through DNA alkylation, producing DNA strand breaks,

thus contributing to synthetic lethality. Therefore, they are widely used in advanced PCa [16], although they do not directly target a specific DNA repair mechanism [2].

8. Biomarkers Predicting Poly-Adenosine Diphosphate Ribose Polymerase Inhibitors Resistance

Unfortunately, neoplastic cells eventually develop resistance mechanisms that overcome the external PARP inhibition and block the pathway of synthetic lethality, as the PARP enzymes become functionable again [1]. The time frame in which resistance develops is usually after 10–18 months of treatment [2]. It usually happens through the mutational reversion of *BRCA1/2*, most frequently due to single-nucleotide alterations that provoke frame shift modifications and result in HR proficiency, preventing the deaths of neoplastic cells [1]. Alternatively, they protect the replication fork to preserve transcription. Other possible resistance mechanisms include the acquisition of genetic alterations in PARP enzymes or the development of efflux pumps that reduce the concentrations of PARP inhibitors within the cancer cells [1]. In a published case report, acquired resistance due to AKT mutation appeared a few months after Olaparib administration and was handled with a concurrent AKT inhibitor [78].

Recent research work proposes that the *MMS22L* gene (which encodes the DNA repair methyl methanesulfonate-sensitivity 22-like protein) is frequently deleted in PCa, mediates HRR and has predictive value regarding PARP inhibitors' effectiveness. The suggested mechanism involves the blockage of the RAD51 molecule, an essential moderator of HRR, in a TP53-dependent way [60]. In contrast, the loss of *CHEK2* has been found to increase the resistance to PARP inhibitors, due to the upregulation of BRCA2, and the concomitant use of PARP and ATR inhibitors could overcome this resistance pathway [60].

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