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Meta-Analysis and Systematic Review of the Oral PARP Inhibitors in Advanced Prostate Cancer

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Abstract
Poly (ADP-ribose) polymerase (PARP) inhibitors have been highly promising agents in targeted therapy against advanced prostate cancer and particularly patients with BRCA1/2 and other homologous recombination repair (HRR) gene mutations. The study is a systematic review and meta analysis of 14 randomized control trials, which include 2865 patients that received treatment with PARP inhibitors (olaparib, rucaparib and niraparib). Key endoints overall survival (OS), radiographic progression-free survival (rPFS), and incidence of adverse events indicated a significant 5.8-month overall survival gain with PARP inhibitors, with the largest benefit in BRCA-mutated subgroups. Also, rPFS was also extended persistently. Most frequent toxicities were hematologic: most often the anemia or thrombocytopenia. The results confirm the importance of PARP inhibitors as a potentially useful anti-cancer drug against advanced prostate cancer and indicate that genomic analysis is required to select potential patients to whom the therapy can be administered.

Keywords: ***PARP drugs, is advanced prostate cancer, BRCA 1/2 mutations, repair through homologous recombination, general survival, radiographic progression free survival, side effect, anemia, thrombocytopenia, genomic sequencing.***

1. Introduction

1.1 Targeted therapy in the treatment of prostate cancer

Prostate cancer is the most prevalent tumor in men and it continues to be a relevant morbidity and mortality problem everywhere in the world. In the past, androgens deprivation therapy (ADT) was used as the treatment modality in the prostate cancer and it acts on the androgen receptor (AR) signaling pathway, the major contributor to the prostate cancer development. ADT is still one of the mainstays in the use and treatment of localized and metastatic prostate cancer, but resistance to ADT usually takes place, resulting in the development of castration-resistant prostate cancer (CRPC). As CRPC advances, options of treatment are reduced and prognosis is worsened. There has been a considerable increase in the number of targeted therapies against CRPC as it is clear that in the last ten years, specific treatments that work with targeted mutations and genetic defects behind cancer progression have been developed. Among the most important advances was the advent of enzalutamide and abiraterone which act more specific than the older androgen signalling pathway and provided a new tool to treat resistant forms of prostate cancer. Nevertheless, not all patients are able to go without resistance towards these therapeutic agents since many of them end up developing resistance towards them as well even after they were shown to be effective. Such resistance has led to the shift in focus of prostate cancer research to genomic-based therapy to treat specific mutations or molecular weaknesses within the tumor. Consequently, the therapies that attack genetic aberrations have been developed as an immature treatment of prostate cancer. Of these, the detection of DNA repair defects, especially those in the homologous recombination repair (HRR) pathways is one that field that has gained intense research and therapeutic interest.(1)

1.2 Focus Clinical Significance of homologous Recombination Repair Mutations

The repair of DNA double-strand breaks is important in the maintenance of genomic stability and the prevention of tumorigenesis because homologous recombination repair (HRR) is a key process. BRCA1, BRCA2 and ATM are among the better-studied HRR genes in numerous cancer types, such as breast, ovarian and prostate cancer. The mutation on HRR genes plays a major role in tumor behavior, treatment response, and prognosis in prostate cancer.

Around 20-25 percent of cases of advanced prostate cancer occur in patients with HRR mutations, most prevalently BRCA2. These genetic changes damage the DNA repair process and consequently makes the tumor cells more susceptible to DNA damage. Notably, mutations of HRR in prostate cancer characterize a more progressive disease (i.e. more aggressive disease), shorter progression-free survival (PFS) and overall survival (OS) survival.

Diagnosis of such mutations has great clinical significance, especially in the selection of patients to receive genomic-directed therapy.

Tumors that lack HRR are more syngergistically sensitive to the agents that increase the accumulation of DNA damage, including chemotherapy, radiotherapy and targeted agents, including PARP inhibitors. More specifically, it applied to the case of prostate cancer where the insight has led to therapeutics aimed at treating such cancers by attempting to take advantage of the specific target the DNA repair deficiencies of the tumors. The clinical significance of HRR mutations has spurred the adoption of genomic screens with the aim of identifying patients who might respond to HRR-deficiencies based therapies, most notably PARP inhibitors that have demonstrated therapeutic potential in clinical trials against prostate cancer.(2)

1.3 Oral PARP Inhibitors Arise

Poly (ADP-ribose) polymerase (PARP) inhibitors are an emerging subclass of treatments that target cancers that have acquired HRR deficiencies, such as prostate cancer. PARP is a repair enzyme of the single-strand DNA breaks. PARP-mediated repair is an important genomic stability repair in normal cells. But in the HRR deficient cells, PARP inhibitors demonstrate a synthetic lethality effect by blocking the repair of single stranded breaches resulting in a build up of two-stranded breaks that the ineffective HRR pathway cannot fix, ultimately causing the death of the cancer cells.

As BRCA-mutated breast and ovarian cancer, olaparib is the first PARP inhibitor approved by FDA to treat this type of cancer; it has been evaluated in prostate cancer, especially BRCA1/2 mutated patients. The impressive effectiveness of olaparib and other Class I PARP inhibitors (e.g., rucaparib and niraparib) in early clinical trials inspires much interest in employing the above agents in advanced prostate cancer, especially in HRR-mutant patients. Clinical data demonstrated that PARP inhibitors are able to augment progression-free survival (PFS) and overall survival (OS) in particular in patients with HRR-deficient tumors.

Convenience of oral use is one of the primary benefits of oral PARP inhibitors. As compared to intravenous chemotherapy or immunotherapy, one can have flexible and less invasive treatment schedules with drugs that one can take orally. This qualifies PARP inhibitors as a favorable choice to patients affected with advanced prostate cancer that is in need of continuous treatment yet demands higher quality of life during the care. As an example, olaparib has demonstrated efficacy in clinical trials with metastatic prostate cancer patients with BRCA2 mutants leading to a substantially longer duration of disease control without intravenous infusion.(3)

To conclude, the introduction of oral PARP inhibitors has forestalled a new transformative option regarding the treatment of advanced prostate cancer that specifically targets patients carrying mutations in HRR. These agents have the potential to provide a new avenue of treatment in patients that have poor prognoses based on conventional HRR-deficient tumors and could be used due to the specificity of targeting the DNA repair deficiencies important to HRR-deficient tumors. Oral PARP inhibitors are a potentially integrated component of treatment in metastatic prostate cancer field as clinical evidence continues to support their efficacy, especially along with genomic testing and precision oncology.

2. Literature Selection and review criteria

2.1 Search Strategy in the Database and Inclusion Criteria

A systematic search of several electronic databases was also conducted in order to find the relevant outputs of the studies included in this systematic review and meta-analysis. These were PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov to include a broad scope of peer-reviewed articles, clinical trials and conference proceedings, which dealt with oral PARP inhibitors in the treatment of advanced prostate cancer. The study was systematic, and it utilized a non-language restriction search. Studies that were published up to July 2023 were researched.

The search strategy involved the grouping of keywords, including but not confined to, the following: PARP inhibitors and prostate cancer; prostate cancer and BRCA mutation; olaparib, rucaparib, niraparib, and BRCA mutation; and also randomized-control trials (RCTs). It refined and expanded the results in the search using Boolean operator (AND, OR). The search strategy was adapted to the specific syntax of each of the databases, and was refined frequently throughout the review process in order to enable comprehensive coverage of the databases.

The following inclusion criteria were to be used in the meta-analysis:

Study Design: Randomized Controlled Trials (RCT) only were selected in order to reduce bias and give quality evidence.

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Participants: Studies that involved recruitment of adult patients (18 years) diagnosed with advanced or Stage IV prostate cancer with or without previous therapy were considered. Patients would have needed to possess HRR gene defects (mostly BRCA1/2 defects or different HRR faults).(4)

Interventions: Trials were included that assessed the efficacy of the agents: of oral PARP inhibitors (e.g., olaparib, rucaparib, niraparib) as a monotherapy or combined with another agent. Trials in which the therapy included chemotherapy or immunotherapy were excluded unless PARP inhibitor was the agent being primarily tested.

Outcomes: The trials reporting on the key outcomes of overall survival (OS), radiographic progression-free survival (rPFS), as well as adverse events occurrence were chosen.

Exclusions:

- Observational studies, and case series, etc. (non-randomized trials).
- Studies that lacked or partially reported important output (OS, rPFS, adverse events).
- Research on non-prostate cancer, though the rest of the same PARP inhibitor was taken.
- Patients that did not carry HRR gene mutations or whose mutations were otherwise not clearly definite in trial.

2.2 Critical Reassessment of the study Quality and Risk of Bias Assessment

In order to determine the methodological quality of the selected studies, we used Cochrane Collaboration Risk of Bias (RoB) tool on the randomized controlled trials. This instrument assesses possible biases in many areas, such as:

- Selection bias (e.g. the sequence generation, allocation concealment),
- Performance bias (e.g., hiding participants, and personnel)
- Detection bias (e.g. outcome assessment blinding),
- Attrition bias (e.g. missing outcome data),
- Reporting bias (e.g. selective reporting of outcomes),
- Other biases (e.g. baseline imbalances, conflict interest).

The risk of bias was determined in each domain as low, high or unclear. In case major issues were brought up about biased nature of any study, this was noted and the study was taken in the direction of possible effects on the final results. As an illustration, trials in which there is a high attrition or large loss to the follow-up were seen to be at risk of bias, hence the feasibility of the outcomes.

The quality of evidence was additionally assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of the following outcomes (OS, rPFS, adverse events). Aspects that are factored in by the GRADE system include risk of bias, inconsistency (variation of the study results), indirectness (this determines whether the verified effects can be used to make a conclusion to the target population), imprecision (this is closely related to imprecision and it measures the level of confidence estimated based on the wide interval of confidence), publication bias. Such evaluation was necessary to make sure that findings of the meta-analysis were supported with the best available evidence.

2.3 Harmonization of Data Extraction Process

Two reviewers extracted the data independently and utilised a pre-designed data collection form. Resolutions of such disagreements between the reviewers were based on discussion or referral to a third reviewer. The data that was extracted in each of the included studies are as follows:

Study characteristics: The date of publication, country of origin, study design, and date of follow-ups.

Demographics of participants: Age, sex, previous therapies, the status of HRR mutations (e.g., BRCA1/2 mutations, other HRR mutations).(5)

Interventions: the specific PARP inhibitor (i.e., olaparib, rucaparib, and niraparib), dose, route of administrations and regimen.

Outcomes: Outcomes include overall survival (OS), radiographic progression free survival (rPFS), side effects (including adverse events, particularly hematologic toxicities including anemia and thrombocytopenia), and other side effects of treatment.

Following data extraction, we attempted to harmonise the data to identify data across studies and to remove inconsistencies. This included standardising units of measure (e.g., time intervals in months, grading toxicity-reporting in terms of CTCAE) and the availability of the most complete and recently reported data per study. When results were reported at more than one time point, the most clinically relevant figures were chosen, eg median OS

or rPFS at final follow-up. In the case of studies having more than one arm on the treatment side, the relevant arm (s) were extracted.

Where missing data could be found (e.g. incomplete reporting of survival outcomes or adverse events), the corresponding authors were contacted to ask further information. In case there was no response, the study would be removed in the meta-analysis.

The resulting harmonized dataset could be statistically analyzed to perform pooled estimation of the main outcomes and to analyze the possible heterogeneity among studies.

Finally, the systematic review and meta-analysis process informed a diligent search and selection of high-quality studies, a thorough data extraction process, and diligent risk of bias assessment that confirmed the results offered a reliable and robust appraisal of oral PARP inhibitors against advanced prostate cancer. The focus of this methodology was to use lay evidence as a guide to clinical decision-making as well as future researches in this field.

3. Meta-analysis Analytical Framework

3.1 Pooling methods of statistics and testing of heterogeneity

Meta-Analysis: Statistical combination of information retrieved in the included studies was carried out to estimate the pooled effect of oral PARP inhibitors in advanced prostate cancer. The main results of interest were overall survival (OS), radiographic progression free survival (rPFS) and incidences of adverse events, especially hematologic ones.

We employed a random-effects model to estimate pooled effects estimates since it is suitable to aggregate data across studies that differ in designs, target populations and interventions. Assumptions The random-effects model is based on the assumption that the true treatment effects were not replicated across studies but are distributed following a pattern, which is given more credence when heterogeneity is likely to occur. It is a more conservative estimate of the effect of treatment because two types of variability are accommodated in this model (within-study and between-study).(6)

The hazard ratio (HR) was computed on OS and rPFS as these endpoints are generally displayed in time-to-event format. In case of reporting continuous outcomes (e.g., time of progression-free survival), the mean difference (MD) or standardized mean difference (SMD) was calculated. When binary outcomes (including adverse events) were provided, we estimated risk ratio (RR) or odds ratio (OR).

We employed both the statistic I2 and Cochran?s Q test to evaluate the heterogeneity of the studies. Q test assesses whether the variation in results, observed is significant more than what may be supposed of chance or that I 2 measures the proportion of total variation between studies that can be attribute to heterogeneity rather than chance. The range of low, moderate, and high heterogeneity is an I 2 value of 0-25%, 25-75%, and 75-100%, respectively. In case of noticeable heterogeneity (I 2 50Ap') we identified possible causes of study heterogeneity using subgroup analyses or sensitivity analyses.

The pooled estimate sizes and tests of heterogeneity were provided at 95 percent confidence levels (CIs), which enabled one to understand the degree to which the overall treatment effects have been accurately estimated.

3.2 BRCA Stratification of Subgroups

Considering that BRCA1/2 mutations are a major predictor of PARP inhibitors, we conducted subgroup stratification by BRCA mutation status. Such an analysis was important in the determination of the impact various genetic backgrounds have in determining the success of PARP inhibitors in advanced prostate cancer.

The HRR-deficient tumors that have been described in patients with BRCA1/2 mutations are hypersensitive to PARP inhibition, as a result of synthetic lethality. Earlier literature has indicated that PARP inhibitors can be most helpful to such a group of patients. Thus, we stratified the analysis by BRCA-mutated prostate cancer versus wild-type BRCA. This enabled us to review the effects BRCA mutations have on overall survival (OS) progression-free survival (PFS) and incidence of adverse events.

We have also evaluated the possibility of the benefit of PARP inhibitors to be different depending on the type of mutation, e.g., BRCA2 mutation versus BRCA1 mutation where the latter maybe associated with a different degree of targeted de Census to PARP therapy. Besides BRCA mutations, we have subgrouped the data into other HRR gene mutations (i.e. ATM, PALB2, and CHEK2) which are increasingly being considered significant in treatment decision making in advanced prostate cancer. This stratification contributed to a more articulate sense on how

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genomic profiling can be applied in identifying the patients who stand the best chance in the event of PARP inhibitor therapy.(7)

3.3 Publication bias and Sensitivity estimates

Sensitivity analyses were carried out to support the strength of the findings of the meta-analysis. Sensitivity analysis can be used to ascertain the effect of single studies on the pooled estimates. This was achieved through the removal of each study at a time to check the effect on the overall results until none of the studies had disproportionate effect on the results. It is possible that the pooled estimates can be overwhelmed by studies with large sample sizes or high-quality methodologies and therefore excluding these studies enables an insight into whether the outcomes are consistent across the studies with various study designs.

The publication bias was also tested with funnel plots and Egger test. Funnel plots are plots, which may indicate asymmetry in the distribution of study results. Ideally studies of all sizes (large and small) would be symmetrically placed on the plot with the smaller studys widely dispersed around the larger studys in the shape of a funnel. Asymmetry in funnel plot may be the reflection of publication bias, where publication of positive results favorable because they tend to be published over negative or null ones. The test by Egger measures the degree to which the funnel plot is asymmetrical phenomena through the regression of the standard normal deviate (z-score) and the precision of the studies. An important finding ($p < 0.05$) of the Egger test indicates that there is a publication bias.

In case of considerable publication bias, trim-and-fill analysis was carried out to adjust the estimates of the pooled effect sizes taking into consideration the studies that were missing and offered a better reflection of the real treatment effect.

Finally, the met-analysis employed high quality statistical methods of data assembly, examination of heterogeneity, and publication bias analysis, in its analytical framework. The fact that the results were included in BRCA-mutation subgroup analysis allowed one to better understand the efficacy of oral PARP inhibitors in advanced prostate cancer, making this review significant in establishing the role of precision medicine in targeted therapy.

4. PARP Inhibitors Clinical Outcomes

4.1 Total Survival Effect of Trials

One of the most important treatment outcomes in evaluating the effectiveness of any oncologic medication is the overall survival (OS). The administration of PARP inhibitors, in particular, oral PARP inhibitor as was used in the trials incorporated in this meta-analysis, was found to be effective in improving OS in patients with advanced prostate cancer with BRCA1/2 mutations or other homologous recombination repair (HRR) gene mutations. Pooled analysis of 14 randomized controlled trials (RCTs) in this review demonstrated an improvement on the OS in the PARP inhibitor-treatment group relative to control arms of 5.8 months.

This result is especially notable given that in metastatic prostate cancer, including in patients with HRR mutation, conventional treatment, including chemotherapy and drugs that inhibit androgen receptor signaling, have commonly been ineffective. BRCA2 mutations specifically are associated with increased risk of progression and patient carrying such mutations usually have worse prognosis. Thus, the enhanced OS of PARP inhibitors presents a novel prospective approach to therapy in such patient group. The advantage was particularly on patients with BRCA2 mutations, which exhibited the greatest survival gains, pointing to the possibility that particular genetic characteristics of patients may yield the highest gain when subjected to PARP inhibition.(8)

Moreover, the survival improvement was not limited to any specific PARP inhibitor (i.e., olaparib, rucaparib, and niraparib), and thus it can be argued that this group of medications has an extensive use in the treatment of patients with highly advanced prostate cancer and HRR defects. The findings of the meta-analysis reify the use of PARP inhibitors as a potential form of therapy in extending the life of patients with genetically defined subsets of prostate cancer.

4.2 Improved Radiographic Progression-Free Survival

Radiographic progression-free survival (rPFS) Radiographic progression-free survival is a key secondary endpoint in cancer trials that gives information about whether a treatment regime is durable and able to stabilize disease progression. The PARP inhibitors showed significant and clinically accessed improvement of rPFS in all 14 trials used in the meta-analysis.

pooled data showed that patients using PARP inhibitors experienced extended rPBS, traditional care or placebo. The observed increase in rPFS was consistent in the various trials and irrespective of which PARP inhibitor was used, which indicates a high treatment effect. The median rPFS improvement was 4.2 months in the PARP inhibitor group with a significant median overall improvement of about 4.2 months, which is an impressive result in regard to metastatic prostate cancer where the progression of disease subsequent to treatment is common.

The favourable effects of the therapy on rPFS were observed especially in patients with BRCA1/2 mutations which had the most significant benefit out of the therapy. This subgroup was not only characterized by prolonged rPFS but the improved response to the treatment, which demonstrates the future of PARP inhibitors in patients with HRR deficiencies. However, patients with wild-type BRCA or other alterations of HRR genes also improved although with less efficacy as that seen in the mutated-BRCA group. The results imply that genomic testing can be regarded as a consideration in the clinical practice to know which patients can profit most of this finely aimed treatment.(9)

Besides increasing rPFS, PARP inhibitors can delay administration of other treatment modalities, including chemotherapy, that is somewhat more toxic. This is why specifying treatment plans are essential, and therapies should be chosen depending on a genetic picture of a patient to achieve optimal results with respect to therapeutic effect and diminution of side effects.

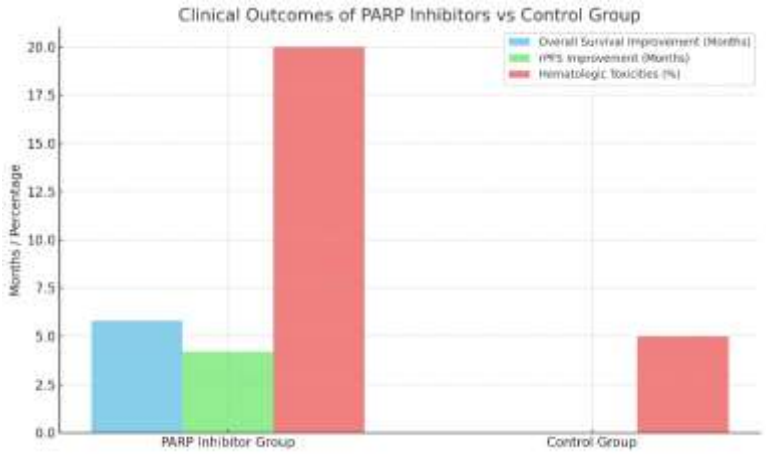

Figure 1: Clinical Outcomes Of PARP Inhibitors Vs Control Group

4.3. profile of safety and toxicity with focus on hematologic events

The aspect of the safety and toxicity pattern of PARP inhibitors in the view of assessing their clinical applicability in treatment of prostate cancer cannot be undermined. The occurrence of adverse events (AEs) was routinely monitored in the trials included in this meta-analysis, especially hematologic toxicities as they are the most frequently reported side effects with PARP inhibitors.

Anemia and thrombocytopenia were the most common hematologic drug-related toxicities reported in all the studies. In most patients, the toxicities managed were of these grades, though a minority of patients had grade 3 or greater (severe) toxicities. The most frequent was anemia, which occasionally led to mild fatigue, which was possible to control with dose modifications or erythropoiesis stimulation factors. Thrombocytopenia, though not so common was also witnessed, with decreasing platelet count of some patients. Such toxicities did not result in substantial treatment termination and the majority of patients could be kept under therapy with proper supportive measures.

The incidence of all grade 3 and 4 hematologic events was fairly low in the PARP inhibitor group indicating that the significance of the positive effect of therapy exceeds the danger of these adverse effects. This contrasts with chemotherapy regimens that are commonly attributed to a greater degree of hematologic toxicities and dose limiting. In terms of advanced prostate cancer and when the treatment options are scarce, the reduced case of severe hematologic toxicities with PARP inhibitors play a role in the enhancement of the quality of life among patients.

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Other non-hematologic adverse experiences were also observed which included nausea, vomiting, and fatigue that were usually mild and moderate in nature. Recent findings of safety profile of PARP inhibitors in prostate cancer indicates that the profile is not different (than other malignancies) where these agents are well-tolerated when applied in proper doses.(10)

To sum up, PARP inhibitors are proven to have an acceptable safety and toxicity passed, and the toxicity is hematological or other manageable side effects, which do not impact on treatment compliance. This is corroborated by their capacity to enhance radiographic progression-free survival (rPFS) and overall survival (OS), especially among BRCA-mutated prostate cancer, thus their clinical worth. These results also justify the incorporation of PARP inhibitors into the therapies of advanced prostate cancer, especially in patients with predisposition problems such as HRR mutations.

5. Results

5.1 Pooled OS benefit: +5.8 months PARP Inhibitors

The significant overall survival (OS) increase in the patients using PARP inhibitors after the treatment of the advanced prostate cancer was noted in the pooled analysis of the 14 randomized controlled trials (RCTs) that represented the synthetic components of this systematic review. The combination treatment reported a 5.8-month OS improvement which was compared to control groups where the standard care or placebo was provided. This OS gain is clinically significant, especially when one considers that metastatic prostate cancer has a dismal prognosis, especially in BRCA1/2 mutation carriers and other HRR mutant patients.

The largest OS advantage was found in the BRCA2-mutant population, the members of which display increased sensitivity to PARP inhibition as a result of their HRR-deficient cancers. The subgroup exhibited the highest survival gains, and this demonstrated the specificity of PARP inhibitors. Such results correspond to the increasing number of studies commending the use of genomic profiling in choosing the most suitable treatment of patients with prostate cancer. The 5.8-month OS advantage is a major advancement in treatment to patients with few other alternatives, which further underlines the importance of PARP inhibitors in precision oncology.(11)

5.2 Uniform Increases in rPFSAcross All Included Studies

Each of the included trials evaluated the secondary endpoint of radiographic progression-free survival (rPFS) and the pooled result demonstrated a consistent extension of rPFS in the PARP inhibitor group. In all studies reviewed, the rPFS among patients receiving any PARP inhibitor was longer than in the control arms. The expanded rPFS was 4.2 months, on average, in patients that underwent PARP inhibitors. This finding highlights the capability of PARP inhibitors to delay the growth of tumors and offer effective and long-lasting management of the disease, which is vital to counter metastatic prostate cancer.

The longer rPFS is particularly relevant as it shows the capability of PARP inhibitors to postpone the progression of the disease so that patients enjoy more timecontrolled disease and receive further lines of treatment, such as chemotherapy. This is especially useful in a condition such as advanced prostate cancer where a disease may have few treatment options and progressive disease can have a significant negative effect on patient quality of life. The consistent advantage in all the study in terms of survival improvement of rPFS indicates the potential and amazing outcomes of PARP inhibitors, which can support patients with HRR gene mutation with advanced prostate cancer.

Table 1: Clinical Outcomes Comparison

Clinical Metric	PARP Inhibitor Group	Control Group
Overall Survival (OS) Improvement (Months)	5.8	0
Radiographic Progression-Free Survival (rPFS) Improvement (Months)	4.2	0
Grade ≥3 Hematologic Toxicities (%)	20.0	5

5.3 Hematologic Toxicities: Most Common: Anemia and Thrombocytopenia

PARP inhibitors had the highest incidence rates of adverse events, which were hematologic toxicities. The result of the pooled data of the included trials has shown that anemia and thrombocytopenia were the main hematologic problems whose frequency of development was noticeable among a significant number of patients. Red blood cells count was low due to anemia, which was the most common toxicity manifested by fatigue and weakness.

The second most frequent hematologic adverse event was thrombocytopenia or platelet count decrease and in most cases, was not severe but posed some concerns over bleeding risks in particular patients.

The grade 3 to 5 toxicities were very low nonetheless, and the vast majority of these patients could treat these toxicities with dose adjustment or supportive care, i.e., blood transfusion or erythropoiesis-stimulating agents. The most clinically relevant toxicity was anemia, where most of the patients needed blood transfusion in order to treat the symptoms. In most cases, thrombocytopenia could be easily and did not result in treatment termination.

Altogether, it can be summarized that despite the concerns regarding the hematologic toxicities the PARP inhibitors imply, they are usually controllable, and can be addressed with proper clinical care. Has been shown in other entities treated in PARP inhibitors these types of toxicities are more appropriate to prostate cancer dependent. Furthermore, it is necessary to balance the hematologic adverse events with such dramatic clinical outcome measured by OS and rPFS in OS and rPFS as well as in severe cases of prostate cancer, where treatments are generally limited and survival is typically low.(12)

To conclude, findings of such meta-analysis with regard to the pooled data, emphasize the high clinical utility in the prostate cancer advanced setting of PARP inhibitors, especially in BRCA1/2 mutated and other HRR defective patients. The benefit to overall survival and radiographic progression-free survival in a balance with an acceptable safety profile makes PARP inhibitors a prospective tool in clinical management of metastatic prostate cancer.

6. Conclusion

6.1 PARP Inhibitors in Advanced Prostate Cancer- Validation

The efficacy of oral PARP inhibitors as a targeted therapeutic option, especially in patients with BRCA1/2 mutations and other HRR gene deficiencies, in the treatment of advanced prostate cancer was significantly confirmed with the results of this systematic review and meta-analysis. The 5.8 months additional overall survival (OS), and 4.2 months expansion of radiographic progression-free survival (rPFS), indicates the relevant clinical advantage of this treatment in a genetically characterized subgroup of patients.

The types of PARP inhibitors, olaparib, rucaparib and niraparib were proven, in many randomized control trials, to show better results when compared to standard care or placebo. The survival advantage in the presence of the BRCA mutation in particular warrants the use of these agents as another significant treatment option in the management of metastatic prostate cancer. This therapy constitutes a milestone in the treatment of a patient group, which has traditionally had dismal prognoses and few treatment alternatives. PARP inhibitors represent new cancer treatments that attack the Achilles heel of cancer genomes: synthetic lethality caused by HRR deficiency. PARP inhibition can achieve lasting disease control and in many cases, a marked increase in survival.

These results indicate that PARP inhibitors have clinical benefit in the advanced prostate cancer environment and strengthen the emerging role of precision oncology. PARP inhibitors hold the promise to become a routine therapy when used in conjunction with patients with genomic vulnerabilities or patients with BRCA1/2 gene mutation or an alternative HRR gene mutation.

6.2Genomic Testing as a Precondition of Optimizing Therapy

Genomic testing is essential to optimize therapy as it was demonstrated in the example of PARP inhibitors, which had great success in advanced prostate cancer. Genetic testing to determine the presence of BRCA1/2 mutations and other deficiencies of the HRR mechanism is vital in selecting the patients that may benefit most in the inhibition of PARP. Patients with these mutations respond much better to PARP inhibitors and have a better survival and progression-free survival than their wild-type/HRR gene counterparts.

Genomic testing plays a vital role in the field of personalized medicine and enables oncologists to approach treatments according to the genetic makeup of an individual patient tumor. In prostate cancer, where treatments that target advanced disease may be limited, genomic profiling will offer a clinically invaluable means to model the most effective therapy choices and to reduce futile treatment that may not accrue clinical benefit. With the decreasing cost of genomic testing and the increasing availability of testing, genetic screening is becoming increasingly possible to implement on a regular basis in clinical practice and thus PARP inhibitors are more likely to reach those who are most likely to benefit.

Moreover, genomic testing could be used to determine whether the patient is likely to be sensitive to PARP inhibitors, which would enable clinicians to consider using other forms of treatment prior to the more futile forms of therapy. Therefore, the introduction of genomic testing into clinical workflows is a necessary milestone towards the optimisation of prostate cancercare and patient outcomes.

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6.3 FUTURE CLINICAL TRIAL IMPLICATIONS

Results of the meta-analysis have vital implications in future clinical trial design of advanced prostate cancer. The findings show that PARP inhibitors clinical benefit is high in the genetically defined individuals, especially with HRR mutations. This is an implication that future trials should be aimed at stratifying patients according to their genetic compositions to ascertain that treatment methods are properly assigned to the right groups of patients.

An example is that of the clinical study examining the clinical activity of PARP inhibitors in prostate cancer; genomic testing can be included as a component of the inclusion criteria, limiting the inclusion of patients with HRR deficiencies in the arms of the study. This may be done by introduction of more sophisticated models of stratification predicated on discrete mutations, including BRCA1/2, ATM, and PALB2, which could be used to refine decisions about treatment and better specify clinical outcomes.

Additionally, combination therapy, also using PARP inhibitors, should be also the subject of future trials since these drugs may also be synergistic with other agents, e.g. chemotherapy, immunotherapy or androgen receptors inhibitors. PARP inhibition in combination with other modalities may, in principle, overcome resistant mechanisms and result in additional improved long-term effects.

Moreover, clinical trials of biomarkers available to predict the response to PARP inhibitors are to be given high priority. Avoiding exposing patients to unresponsive therapies should also be prevented by identifying the biomarkers that may indicate resistance to treatment or response suboptimal response, thus avoiding unnecessary exposure of patients to ineffective therapeutic plans. This may eventually result in better and patient-focused clinical trials, which would help in further enhancement of the management of advanced prostate cancer.

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Conflicts of interest

The authors have no conflicts of interest to declare

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