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SYSTEMATIC REVIEW

Hematological Toxicity of PARP Inhibitors in Metastatic Prostate Cancer Patients with Mutations of *BRCA* or *HRR* Genes: A Systematic Review and Safety Meta-analysis

Brigida Anna Maiorano[1] · Ugo De Giorgi[2] · Elena Verzoni[3] · Evaristo Maiello[1] · Giuseppe Procopio[3] · Vincenza Conteduca[4] · Massimo Di Maio[5] on behalf of the MeetURO group

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Abstract

Background PARP inhibitors (PARPis) are effective treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC) as single agents or in combination with androgen receptor-targeted agents (ARTA). However, a clinically relevant adverse effect of these agents is hematological toxicity, a typical class adverse event (AE), which can lead to treatment modifications and discontinuations.

Objective We aimed to analyze the risk of hematological AEs, including anemia, neutropenia, and thrombocytopenia secondary to PARPi treatments in mCRPC.

Patients and Methods This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. We systematically searched the PubMed, EMBASE, and Cochrane databases, the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) meeting abstracts for clinical trials concerning the use of PARPis, both as single agents and in combination, in patients with mCRPC. The search deadline was 30 June, 2023. We analyzed the pooled incidence of all grades of and ≥ G3 anemia, neutropenia, and thrombocytopenia. We subsequently calculated risk ratios (RRs) for all grades of and ≥ G3 AEs of PARPis versus non-PARPis from randomized clinical trials (RCTs).

Results Eleven phase 2/3 trials with olaparib, niraparib, rucaparib, and talazoparib administered as single agents or combined with ARTA were selected. Anemia was the most common all grades (38.6%) and ≥ G3 AE (24.9%). In the analysis of relative risk, six RCTs were included. The administration of PARPis significantly increased the risk of developing all grades of anemia (RR = 2.44), neutropenia (RR = 3.15), and thrombocytopenia (RR = 4.66) compared with non-PARPis. Similarly, a significant increase in the risk of ≥ G3 anemia (RR = 5.73) and thrombocytopenia (RR = 5.44), and a not significant increased risk of neutropenia (RR = 3.41), were detected.

Conclusions In mCRPC, PARPis increase the risk of hematological toxicity compared with other treatments, both as single agents or combined with ARTA (high-quality evidence). Clinicians should be aware of this risk and the correct management, especially with the expected increased PARPis use in mCRPC.

1 Introduction

Prostate cancer is the most common tumor and the second leading cause of cancer-related death in males [1]. In the setting of metastatic castration-resistant prostate cancer (mCRPC), despite the availability of several agents, such as chemotherapy (CHT)—mainly represented by the taxanes family—and androgen receptor-targeted agents (ARTA), there is a need to improve survival and response rates [2]. In fact, up to one out of four patients with mCRPC carries mutations in homologous recombination repair (*HRR*) genes, mainly breast cancer-related gene (*BRCA*) 1 and 2 (8–10%), with a negative prognostic role for survival and disease progression and potential sensitivity to poly-ADP ribose polymerase (PARP) inhibitors (PARPis) [3–6].

In 2020, PARPis entered the therapeutic path of mCRPC, starting with the US Food and Drug Administration (FDA) approval of olaparib for patients with germline or somatic mutations of HRR genes, progressing to ARTA

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Key Points

PARP inhibitors have been approved for metastatic prostate cancer; however, they typically have blood toxicity, often leading to dosage modification or interruption.

Our meta-analysis found that PARP inhibitors significantly increased the risk of anemia, neutropenia, and thrombocytopenia, and severe anemia and neutropenia, compared with other treatments, in patients with metastatic prostate cancer.

We should warn clinicians of this risk to manage patients correctly, because there are many ongoing studies with PARP inhibitors, and their use is expected to rise in the next years.

after the results of the phase 3 PROfound trial, in which olaparib prolonged overall survival (OS) up to 19.1 versus 14.7 months compared with the alternative ARTA [hazard ratio (HR) 0.69, $p = 0.02$] [7–10]. The European Medical Agency (EMA) restricted the approval only for BRCA1/2-mutated patients with mCRPC [11]. Subsequently, rucaparib was approved by FDA as monotherapy for treating patients with mCRPC [12, 13]. More recently, three combinations of PARPis and ARTA have been approved after improving survival and responses in randomized clinical trials (RCT): abiraterone + olaparib, niraparib + abiraterone, and talazoparib + enzalutamide [7, 11, 14–17]. The current FDA and EMA indications are presented in Table 1.

PARPis are associated with characteristic class adverse events (AEs), such as hematological toxicity, often representing a reason for dosage modification, interruption, or discontinuation, or need for supportive cares such as transfusions [18–20]. These effects can be challenging in a population such as mCRPC, where patients are often pretreated with CHT carrying a risk of hematological toxicity, having a relevant bone disease burden, or with elderly age at diagnosis linked to high frailty. Based on these premises, we performed a systematic review and meta-analysis to evaluate the hematological toxicity of PARPis in mCRPC.

2 Materials and Methods

2.1 Data Retrieval Strategies and Extraction

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21 PRISMA]. In June 2023, two authors independently searched the literature using the MEDLINE/PubMed, Embase, and Cochrane databases with no data restriction. An additional search for meeting abstracts from the ASCO and European Society of Medical Oncology (ESMO) was performed. A crosscheck reference from review articles was also conducted for all possible pertinent data retrieval. The following terms were used: ("PARP inhibitor" OR "PARP inhibitors" OR olaparib OR niraparib OR veliparib OR rucaparib OR talazoparib) AND ("prostate cancer" OR "prostate carcinoma" OR prost*).

Full texts and conference abstracts were examined, and citations for candidate studies using a predefined information list were screened. For each eligible study, the following data were independently extracted: study characteristics (authors' names, year of publication, clinical trial name, phase, design, randomization), population (setting, sample size, patients' demographics), description of interventions (drug, dosage, and combinations), and safety data (number, type and grade of hematologic AEs). Two authors conducted data collection independently, and discrepancies were resolved by consensus.

Table 1 Summary of PARPis approvals by the FDA and EMA regulatory agencies

PARPi	FDA indication	EMA indication
Olaparib	Deleterious or suspected deleterious germline/somatic HRR-mutated mCRPC, after progression to an ARTA	Somatic/germline BRCA1/2-mutated mCRPC after progression to an ARTA
Olaparib + abiraterone	Deleterious or suspected deleterious BRCA-mutated mCRPC	Naïve mCRPC not eligible for chemotherapy
Niraparib + abiraterone	Deleterious or suspected deleterious BRCA-mutated mCRPC	Somatic/germline BRCA1/2-mutated mCRPC not eligible for chemotherapy
Talazoparib + enzalutamide	HRR-mutated mCRPC	–
Rucaparib	Somatic/germline BRCA1/2-mutated mCRPC progressing to ARTA and a taxane	–

ARTA androgen receptor-targeted agent, *BRCA1/2* breast cancer-related gene 1/2, *EMA* European Medical Agency, *FDA* US Food and Drug Administration, *HRR* homologous recombination repair, *mCRPC* metastatic castration-resistant prostate cancer, *PARPi* poly-ADP ribose polymerase inhibitor

2.2 Population, Outcomes of the Analysis, Included Studies

Eligible studies were: (1) prospective phase II and III clinical trials, (2) conducted in patients with mCRPC, (3) conducted using PARPis (laparib, niraparib, rucaparib, talazoparib), and (4) reporting data of hematological toxicity, more specifically anemia, neutropenia, and thrombocytopenia. Reviews, commentaries, letters, personal opinions, preclinical studies, case reports, and studies that did not report the outcome data and/or with sample size < 10 participants were excluded. The research was restricted to the English language.

Patients of the experimental group were treated with PARPis single agent or combined with other drugs such as ARTA. In the control group, patients did not receive PARPis, whereas other drugs (e.g., ARTA, chemotherapy) or placebo (PBO) were administered.

Hematological safety was explored as the number and grade [all grades and greater than grade 3 (≥ G3)] of AEs: anemia, neutropenia, and thrombocytopenia. In the meta-analysis, all grades and ≥ G3 anemia, neutropenia, and thrombocytopenia represented the analyzed outcomes.

2.3 Risk of Bias Assessment

Two reviewers independently assessed the risk of bias. The Cochrane tool for the bias risk was used [22].

2.4 Data Synthesis and Statistical Analysis

We extracted the number of patients developing the specific AE for calculating the incidence of all grades and ≥ G3 AEs. The proportion of patients and the corresponding 95% confidence intervals (95% CI) were calculated. For comparing the risk of hematological AEs with PARPis and without PARPis, risk ratios (RRs) with 95% CIs were calculated. The summary estimates were generated using the generic inverse variance and a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird method), depending on the absence or presence of heterogeneity [23, 24]. The presence of heterogeneity between the studies was assessed through the χ^2 test and I^2 statistic. I^2 values of 25%, 50%, and 75% were established for low, moderate, and high heterogeneity, respectively. When $I^2 < 50\%$, the fixed-effects model was used; otherwise, the random-effects model was used [25]. Subgroup analyses were planned to detect the underlying source of heterogeneity between the studies in terms of agent name (olaparib, niraparib, rucaparib, talazoparib), treatment regimens (PARPi given as a single agent versus combination), and disease setting (naïve for CRPC versus pretreated patients). A sensitivity analysis was performed to assess the stability of the global estimate by moving away one study at a time. No correction for multiplicity was applied. The statistical significance was considered in the case of p value < 0.05 (all tests were two-sided). R studio v.3 was used for performing the statistical analysis.

2.5 Assessment of Evidence Certainty

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to assess the certainty of the evidence through a non-contextualized approach, including the risk of bias, inconsistency of the effect, indirectness, imprecision, and publication bias. A GRADE Summary of Findings graphic was developed using the GRADEpro Guideline Development Tool platform (www.gradepro.org).

3 Results

3.1 Search Results

The research identified 725 studies from databases and conference abstracts. After duplicate removal, 710 papers were screened. Among them, 690 papers were excluded for non-English language, preclinical articles, or reviews. After considering only RCTs, six studies were included in the meta-analysis at the end of the selection process. The PRISMA flow chart summarizing the selection process is presented in Fig. 1.

3.2 Characteristics of the Included Studies

In the qualitative analyses, we selected eleven studies [9, 10, 12–18, 27–33]. Among them, there were four single-arm open-label (SA–OL) phase II studies, including a total of 581 pretreated patients with mCRPC in the safety population, receiving olaparib ($n = 1$), niraparib ($n = 1$), talazoparib ($n = 1$), and rucaparib ($n = 1$) [12, 13, 26, 28, 29]. One phase II RCT was considered only in the qualitative synthesis, as it included olaparib in the experimental and control groups, given at different dosages, for a total of 49 patients per arm in the safety population [29]. The other six RCTs were also included in the quantitative meta-analysis [9, 10, 14–18, 31–33]. Among them, there were three phase II and three phase III trials. In two studies, olaparib and rucaparib were administered as single agents in the experimental arm and compared respectively with ARTA and ARTA/taxane in the control arm [9, 10, 33]. In four studies, PARPis were combined with ARTA in the experimental arm, and

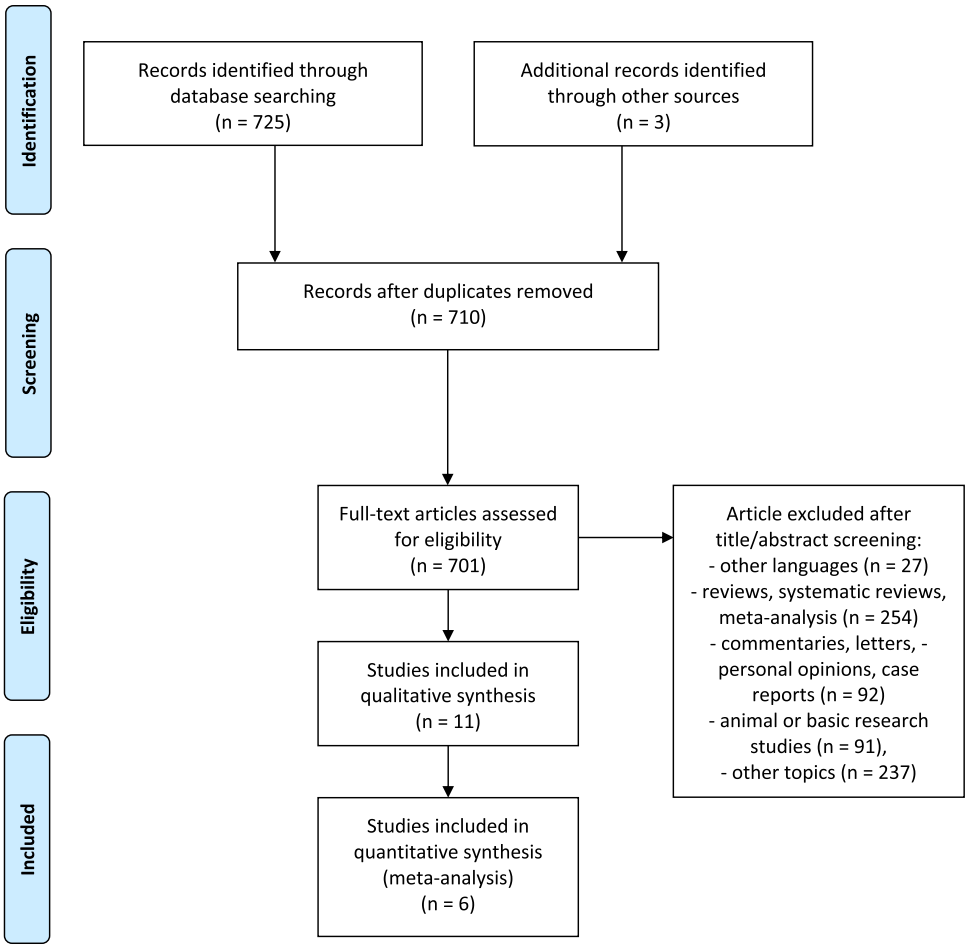


Fig. 1 PRISMA flowchart of the selection process

compared with PBO plus ARTA in the control group: olaparib plus abiraterone ($n = 2$), niraparib plus abiraterone ($n = 1$), and talazoparib plus enzalutamide ($n = 1$) [14–17, 30, 31]. Overall, 1605 patients represented the safety population treated with PARPis in the experimental arm (526 as monotherapy) and 1339 patients in the control group (260 as monotherapy). In the different studies, eligible patients should have a minimum of 10.0 g/dL of hemoglobin, 1.5 x 10^9/L absolute neutrophils count, and 100×10^9/L platelets. No significant risk of bias was evidenced (Supplementary Fig. 1).

The main characteristics of the included studies are listed in Table 2.

3.3 Incidence Rate of Hematological AEs

Among all grades of AEs, anemia was the most common (38.6%), followed by neutropenia (12.0%) and thrombocytopenia (14.3%). As for ≥ G3 toxicities, again, anemia presented most frequently (24.9%), followed by thrombocytopenia (8.0%) and neutropenia (5.0%) (Table 3).

3.4 Risk of Hematological AEs of PARPis Compared to Non-PARPis

Patients treated with PARPis had a significantly higher risk of all grades of anemia than those not receiving PARPis (RR = 2.44; 95% CI, 1.54–3.84; $p = 0.0001$). The use of PARPis significantly also increased the risk of neutropenia (RR = 3.15; 95% CI, 1.58–6.27; $p = 0.008$) and thrombocytopenia (RR = 4.66; 95% CI, 1.62–13.38; $p = 0.004$). All analyses had a statistically significant heterogeneity among the studies (Fig. 2A–C).

3.5 Risk of Severe Hematological AEs of PARPis Compared with Non-PARPis

Patients receiving PARPis were at a significantly higher risk of ≥ G3 anemia (RR = 5.73; 95% CI 2.72–12.04; $p < 0.00001$), with significant heterogeneity among the studies ($I^2 = 81\%$; $p < 0.0001$). Moreover, they tended to have a higher risk of ≥ G3 neutropenia (RR = 3.41; 95% CI 0.71–16.37; $p = 0.13$), with significant

Table 2 Characteristics of the included studies

Trial	First author	Year	Phase	Design	Disease setting	Treatment	No. of patients (safety)	Median treatment duration (months)
Single agents								
PROfound (NCT02987543) [9]	de Bono J	2020	3	RCT	mCRPC (pretreated with ARTA)	Olaparib ARTA	256 130	37.2
TRITON2 (NCT02952534) [12, 13]	Abida W	2020	2	SA–OL	mCRPC (pretreated with ARTA and Txt)	Rucaparib	115	6.5
TOPARP-A (NCT01682772) [26]	Mateo J	2015	2	SA–OL	mCRPC (pretreated with CHT)	Olaparib	50	3.0
TOPARP-B (NCT01682772) [27]	Mateo J	2020	2	RCT*	mCRPC (pretreated with taxanes)	Olaparib 300 mg Olaparib 400 mg	49 49	NA
TALAPRO-1 (NCT03148795) [28]	de Bono J	2021	2	SA–OL	mCRPC (pretreated with ARTA and Txt)	Talazoparib	127	6.1
GALAHAD (NCT02854436) [29]	Smith MR	2022	2	SA–OL	mCRPC (pretreated with ARTA and Txt)	Niraparib	289	6.7
TRITON3 (NCT02975934) [32]	Fizazi K	2023	3	RCT	mCRPC (pretreated with ARTA)	Rucaparib ARTA/Txt	270 130	8.3 5.1
Combinations								
PROpel (NCT03732820) [15]	Clarke NW	2022	3	RCT	mCRPC (naïve)	Olaparib + abiraterone PBO + abiraterone	398 396	17.5 15.7
TALAPRO-2 (NCT03395197) [16]	Agarwal N	2023	2	RCT	mCRPC (naïve)	Talazoparib + enzalutamide PBO + enzalutamide	398 401	19.8 16.2
NCT01972217 [30]	Clarke NW	2018	2	RCT	mCRPC (pretreated with Txt)	Olaparib + abiraterone PBO + abiraterone	71 71	10.1 8.3
MAGNITUDE (NCT03748641) [31]	Chi KN	2022	3	RCT	mCRPC (naïve)	Niraparib + abiraterone PBO + abiraterone	212 211	NA

ARTA androgen receptor-targeted agent, *CHT* chemotherapy, *mCRPC* metastatic castration-resistant prostate cancer, *NA* not available, *PBO* placebo, *RCT* randomized clinical trial, *SA–OL* single-arm open-label, *Txt* Taxotere

*This RCT was excluded from the meta-analysis. See below for explanations

Table 3 Pooled incidence of hematologic AEs of PARP-inhibitors in mCRPC

Hematologic AE	Incidence rate, % (95% CI)
Anemia	38.6% (37.5–39.8)
Neutropenia	12.0% (11.6–12.4)
Thrombocytopenia	14.3% (13.5–15.1)
≥ G3 anemia	24.9% (24.1–25.6)
≥ G3 neutropenia	5.0% (4.7–5.3)
≥ G3 thrombocytopenia	8.0% (7.0–9.0)

AE adverse event, *CI* confidence interval, ≥ *G3* equal to over grade 3

heterogeneity among the included studies (I^2 = 90%; p < 0.0001). Patients were also at a higher risk of ≥ G3 thrombocytopenia (RR = 5.44; 95% CI 2.76–10.73; p < 0.00001). In this analysis, the studies were homogeneous (Fig. 3A–C).

3.6 Subgroup and Sensitivity Analysis

To explore the sources of heterogeneity, we performed subgroup analyses according to drug type (olaparib, niraparib, rucaparib, talazoparib), PARPis monotherapy versus combination, and disease setting (naïve versus pretreated patients). The administered PARPi influenced the all grades of AEs, ≥ G3 anemia and neutropenia results. The ≥G3 neutropenia RR was different when PARPis were used in combination rather than as single agents (Table 4).

The sensitivity analysis showed no differences in the results after removing one study at a time, except all grades of thrombocytopenia, which was mainly influenced by the

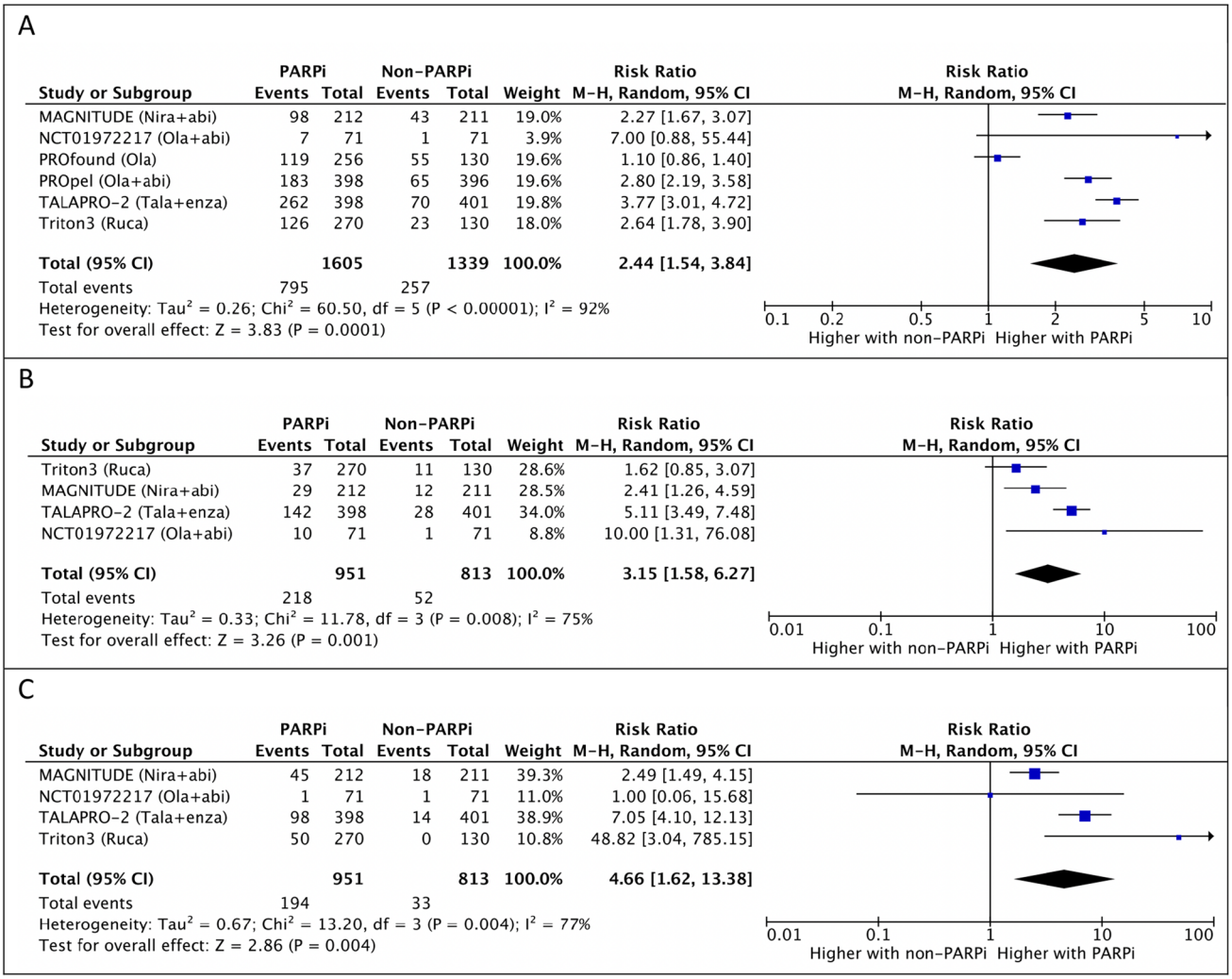


Fig. 2 Relative risk of all grades of anemia (**A**), neutropenia (**B**), and thrombocytopenia (**C**) of PARPis compared with non-PARPis in mCRPC

TALAPRO-2 study, and ≥ G3 neutropenia that was influenced by MAGNITUDE and TALAPRO-2 studies (Supplementary Fig. 2 A–F).

4 Discussion

4.1 Summary of Findings

PARPis have emerged as one of the most exciting targeted therapies for prostate cancer. Since 2020, PARPis have been approved by the Regulatory Agencies for clinical use in mCRPC, namely olaparib, rucaparib, niraparib, and talazoparib [7, 8, 11] (Table 1). Our systematic review and safety meta-analysis focuses explicitly on the mCRPC setting, reporting a higher incidence rate for hematological AEs of all grades and severe grades when PARPis are administered as single agents or combined with different treatments.

Regarding all grades of AEs, the administration of PARPis in mCRPC increases the risk of developing anemia (RR 2.44), with an absolute effect of 468 versus 192 events every 1000 patients. PARPis increase the risk of developing neutropenia (RR 3.15), with an absolute effect of 201 versus 64 events every 1000 patients, and thrombocytopenia (RR 4.66), with an absolute effect of 189 versus 41 every 1000 patients. Referring to severe AEs, PARPis increase the risk of developing ≥ G3 anemia (RR 5.73, absolute effect of 231 versus 40 every 1000 patients), neutropenia (RR 3.41, absolute effect of 97 versus 28 every 1000 patients), and thrombocytopenia (RR 5.44, absolute effect of 60 versus 11 every 1000 patients). Considering the GRADE considerations, we judged the quality of the evidence as high for all the outcomes. Therefore, we are

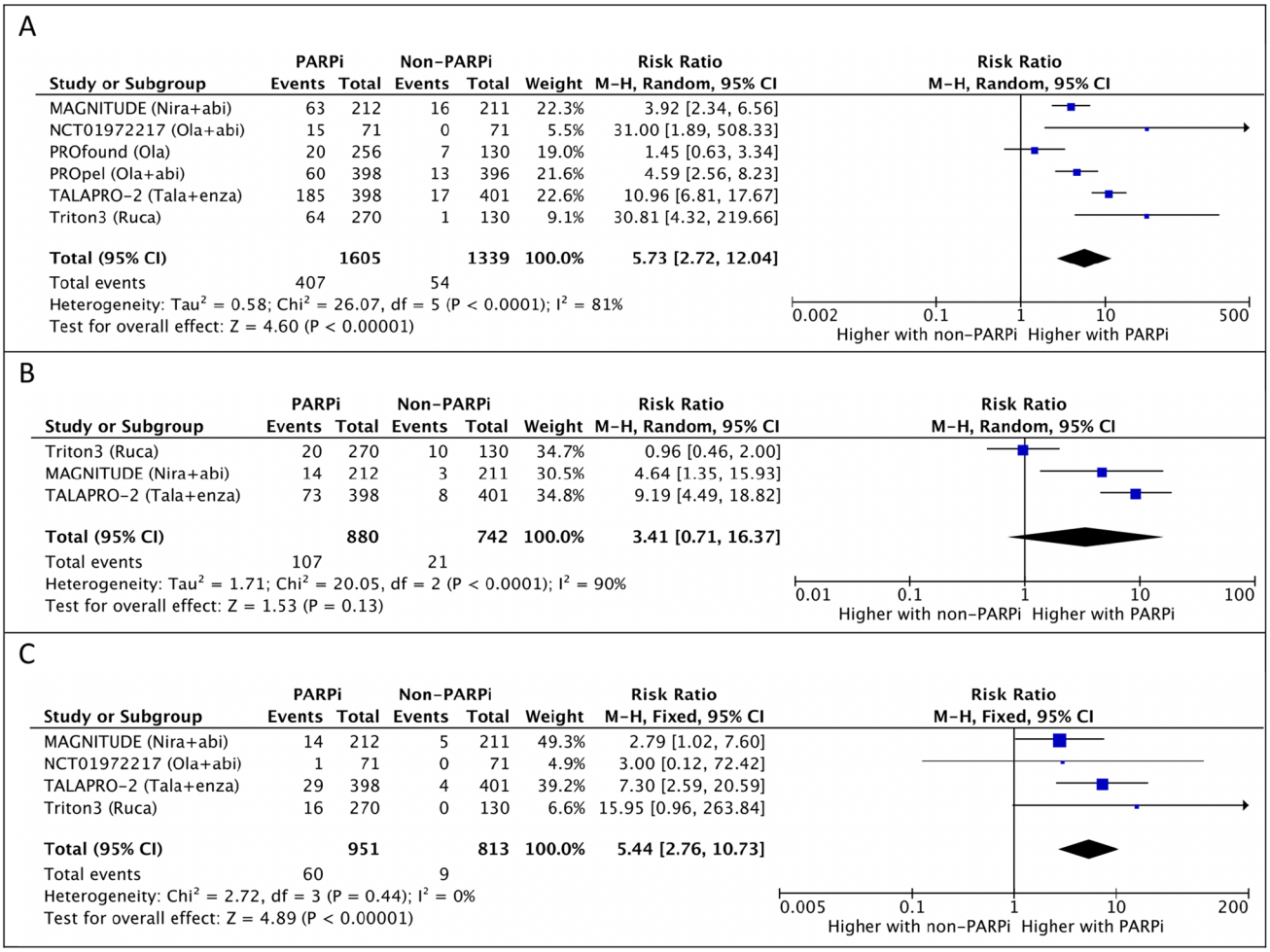


Fig. 3 Relative risk of ≥ G3 anemia (**A**), neutropenia (**B**), and thrombocytopenia (**C**) of PARPis compared with non-PARPis in mCRPC

confident that the true effect on AEs lies close to that of the estimated effect (Fig. 4).

4.2 Implications for Clinical Practice and Future Directions

Hematological toxicity is frequently reported in other tumor subtypes as an on-target class effect of PARPis, mainly depending on PARP trapping and BRCA2 expression by erythroid progenitors [33–40]. Olaparib and rucaparib had a > 100-fold half-maximal inhibitory concentration (IC_{50}) between PARP inhibition and bone marrow toxicity, whereas talazoparib was only two-fold as the therapeutic effect of the latter lies close to the toxic activity [34–36]. Effectively, in our subgroup analysis, the higher RR for anemia was attributable to talazoparib, even if more studies are needed to explore this evidence further. In the studies, most hematological toxicity depended on PARPis: indeed, enzalutamide and abiraterone in the control groups definitely showed a lower risk of anemia, ranging from 16% to 22% (0–8.5% as ≥ G3 anemia). In the TALAPRO-2, a median hemoglobin decrease of 2 g/dL was recorded in the talazoparib + enzalutamide group. This led to 13.1% of patients receiving red blood cell transfusions, with 8.3% receiving erythropoietin-stimulating agents [16, 17].

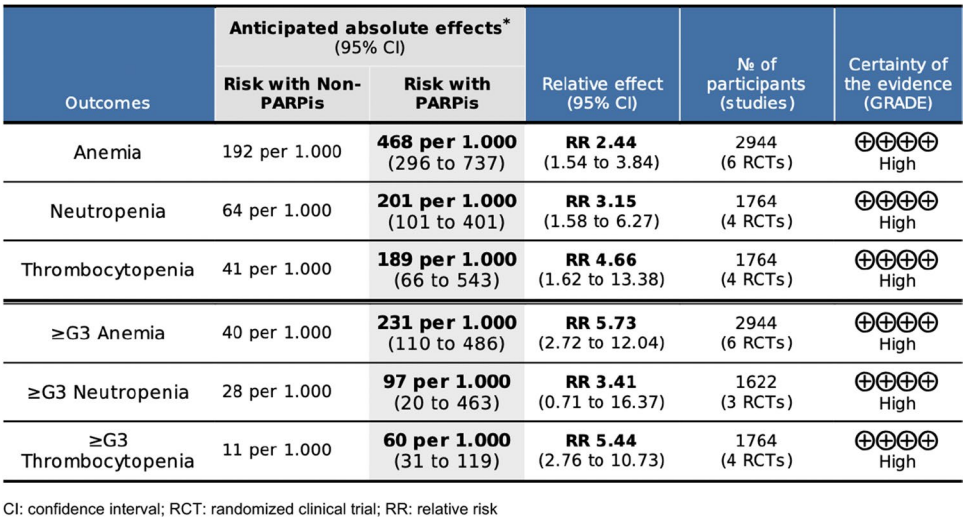
Similar to other tumor subtypes, in mCRPC, hematologic AEs tend to occur early after PARPis starts, recovering after a few months [33–40]. Currently, no specific explanation has been found for this phenomenon. In the PROfound trial, hematologic AEs peaked within the first 2 months of olaparib start and lasted for a further 2 months. Anemia often led to olaparib interruption (26%), reduction (16%), and discontinuation (8%) [9, 10]. In the TALAPRO-2 study, ≥ G3 hematologic AEs occurred within 6 months of talazoparib starting (median 3.3 months for anemia, 2.3 for neutropenia and thrombocytopenia) and usually resolved in

Table 4 Subgroup analyses for hematological toxicity of PARPis in mCRPC

Subgroup	Anemia, RR (95% CI)	Neutropenia, RR (95% CI)	Thrombocytopenia, RR (95%CI)	≥ G3 anemia, RR (95%CI)	≥ G3 neutropenia, RR (95% CI)	≥ G3 thrombocytopenia, RR (95% CI)
Drug name						
Olaparib	2.10 (0.87–5.05)	10.00 (1.31–76.08)	1.00 (0.06–15.68)	3.69 (1.13–12.07)	/	3.00 (0.12–72.42)
Niraparib	2.27 (1.67–3.07)	2.41 (1.26–4.59)	2.49 (1.49–4.15)	3.92 (2.34–6.56)	4.64 (1.35–15.93)	2.79 (1.02–7.60)
Rucaparib	2.64 (1.78–3.9)	1.62 (0.85–3.07)	48.82 (3.04–785.15)	30.81 (4.32–219.66)	0.96 (0.46–2.00)	15.95 (0.96–263.84)
Talazoparib	3.77 (3.01–4.72)	5.11 (3.49–7.48)	7.05 (4.10–12.13)	10.96 (6.81–17.67)	9.19 (4.49–18.82)	7.30 (2.59–20.59)
Subgroup differences	***P* = 0.04**	***P* = 0.009**	***P* = 0.009**	***P* = 0.009**	***P* < 0.0001**	*P* = 0.47
Disease setting						
Naive	2.91 (2.19–3.90)	3.67 (1.76–7.65)	4.17 (1.48–11.79)	5.88 (3.00–11.52)	3.67 (1.76–7.65)	4.47 (1.72–11.63)
Pre-treated	2.01 (0.85–4.78)	3.13 (0.54–18.13)	6.96 (0.09–545.43)	9.65 (0.54–173.42)	3.13 (0.54–18.13)	7.68 (0.94–63.07)
Subgroup differences	*P* = 0.42	*P* = 0.87	*P* = 0.82	*P* = 0.74	*P* = 0.87	*P* = 0.65
PARPis mono versus combo						
Monotherapy	1.68 (0.69–1.40)	1.62 (0.85–3.07)	48.82 (3.04–785.15)	6.13 (0.15–249.04)	0.96 (0.46–2.00)	15.95 (0.96–263.84)
Combination	2.97 (2.25–3.92)	4.04 (2.11–7.72)	3.62 (1.38–9.49)	6.38 (3.29–12.39)	7.74 (4.16–14.37)	4.36 (2.16–8.80)
Subgroup differences	*P* = 0.23	*P* = 0.05	*P* = 0.08	*P* = 0.98	***P* < 0.0001**	*P* = 0.38

Statistically significant differences are bolded

CI confidence interval, *≥ G3* equal to over grade 3, *RR* relative risk



Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Non-PARPis	Risk with PARPis			
Anemia	192 per 1.000	**468 per 1.000** (296 to 737)	**RR 2.44** (1.54 to 3.84)	2944 (6 RCTs)	⨁⨁⨁⨁ High
Neutropenia	64 per 1.000	**201 per 1.000** (101 to 401)	**RR 3.15** (1.58 to 6.27)	1764 (4 RCTs)	⨁⨁⨁⨁ High
Thrombocytopenia	41 per 1.000	**189 per 1.000** (66 to 543)	**RR 4.66** (1.62 to 13.38)	1764 (4 RCTs)	⨁⨁⨁⨁ High
≥G3 Anemia	40 per 1.000	**231 per 1.000** (110 to 486)	**RR 5.73** (2.72 to 12.04)	2944 (6 RCTs)	⨁⨁⨁⨁ High
≥G3 Neutropenia	28 per 1.000	**97 per 1.000** (20 to 463)	**RR 3.41** (0.71 to 16.37)	1622 (3 RCTs)	⨁⨁⨁⨁ High
≥G3 Thrombocytopenia	11 per 1.000	**60 per 1.000** (31 to 119)	**RR 5.44** (2.76 to 10.73)	1764 (4 RCTs)	⨁⨁⨁⨁ High

CI: confidence interval; RCT: randomized clinical trial; RR: relative risk

Fig. 4 Summary of findings of the included studies for all grades of and ≥ G3 hematological adverse events of PARPis compared with non-PARPis in mCRPC

the first month. A total of 19.1% of patients discontinued talazoparib due to AEs [16, 17]. Anemia was more consistently the leading cause of treatment interruption (44.2%), reduction (43.2%), and discontinuation (8.3%) [41]. Notably, a high bone disease burden, which often characterizes patients with mCRPC, previous treatments with bone marrow toxicity such as taxanes, advanced age at diagnosis, and comorbidities could contribute to the onset and worsening of anemia and other hematologic AEs in these patients. As the FDA and other societies recommend, all patients starting PARPis should have a complete blood count at least monthly. In the case of niraparib, this monitoring should be done weekly in the first month [7, 11].

Table 5 Ongoing studies of PARPis in mHSPC

Clinical trial name	Phase	Experimental arm	Control arm	Target number
TALAPRO-3 (NCT04821622)	3	Talazoparib + enzalutamide	PBO + enzalutamide	550
AMPLITUDE (NCT04497844)	3	Niraparib + abiraterone	PBO + abiraterone	788
ZZ-First (NCT04332744)	2	Talazoparib + enzalutamide	–	54

PBO placebo

Hematological safety should be even more carefully considered in the followingyears when the use of PARPis is expected to rise, and they will be combined with other drugs in earlier disease settings. In fact, studies are ongoing in metastatic hormone-sensitive prostate cancer (mHSPC), and results expected in the coming months could allow us to change our clinical practice and anticipate the use of PARPis in this disease (Table 5).

*BRCA*1/2 mutations are also demonstrated in mHSPC and are associated with shorter time to mCRPC and overall survival [3–6]. The studies listed in Table 4 are combination studies with a PARPi and either abiraterone or enzalutamide. Our analysis of these combinations in mCRPC showed no significant differences compared with monotherapy in all grades and severe hematological toxicities (except ≥ G3 neutropenia), suggesting these combinations should be well tolerated in mHSPC.

To our knowledge, this is the first qualitative and quantitative synthesis of hematological AEs of PARPis specifically addressing patients with mCRPC. The results of our analysis on patients with mCRPC confirm previous data regarding other tumor subtypes. A strength of this analysis is the systematic approach to reviewing all the published trials with quantitatively meta-analyzed RCTs, resulting in a large number of analyzed patients. Limitations of our study are represented firstly by the heterogeneity of the studies in terms of different PARPis and settings, monotherapy versus combinations, and comparator arms. We cannot compare germline and somatic mutations or *BRCA* versus *HRR* genes due to a lack of information in the included studies, even though we could not expect differences between the groups regarding safety. Still, this analysis could have helped to clarify the risk–benefit ratio, especially in populations for which PARPis efficacy is unclear, such as *HRR* negative patents. Moreover, we must consider that patients in worse general conditions were not included in the clinical trials; therefore, the real impact of hematologic AEs in the daily clinical practice could be more relevant, and this consideration should be taken into account in a population, such as the mCRPC, often of advanced age and multiple comorbidities. Further ongoing RCTs will better help to clarify the real impact of hematological AEs of PARPis compared with different treatment strategies. Finally, another limitation of our meta-analysis is the use of aggregate rather than individual data.

5 Conclusions

In conclusion, our analysis highlights the hematological toxicities of PARPis alone and in combination with ARTA. Clinicians and patients should be aware of this risk, and the need for regular monitoring of blood counts. Results of the ongoing studies and updates of the published trials could better distinguish the specific toxicity profile of the different PARPis available for patients with prostate cancer.

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Declarations

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Authors and Affiliations

Brigida Anna Maiorano[1] · Ugo De Giorgi[2] · Elena Verzoni[3] · Evaristo Maiello[1] · Giuseppe Procopio[3] · Vincenza Conteduca[4] · Massimo Di Maio[5] on behalf of the MeetURO group

✉ Brigida Anna Maiorano
b.maiorano@operapadrepio.it; brigidamaiorano@gmail.com

[1] Oncology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

[2] Department of Medical Oncology, IRCCS Istituto Romagnolo Per Lo Studio Dei Tumori (IRST) "Dino Amadori", Meldola, Italy

[3] Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

[4] Unit of Medical Oncology and Biomolecular Therapy, Department of Medical and Surgical Sciences, University of Foggia, Policlinico Riuniti, Foggia, Italy

[5] Division of Medical Oncology, Department of Oncology, University of Turin, Turin, Italy