Analysis of clinical factors in olaparib-related anemia using adverse drug event reporting databases

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Research Article

Abstract

Purpose: Anemia is one of the dose-limiting toxicities of olaparib. The global phase trial confirmed that anemia occurrence in Japanese was relatively high. The factors related to anemia in different nationalities remain unknown. Therefore, this study investigated the factors of olaparib-related anemia in real-world settings using an adverse event reporting system database.

Methods: We used data from FDA Adverse Events Reporting System (FAERS) and Japanese Adverse Drug Event Report database (JADER) between 2018 and 2021. FAERS reports from Japan were collected to conduct subgroup analyses, which was defined as FAERS-Japan. The endpoint was the occurrence of olaparib-related anemia. Disproportionality analysis was conducted to calculate reporting odds ratio (ROR), with a confidence interval of 95%. Adjusted ROR (aROR) was calculated to control for gender differences.

Results: In FAERS and JADER, the daily olaparib dose per body weight (DPBW) ≥12 mg/kg was detected to be a positive signal for anemia occurrence (aROR; FAERS, 4.483 [3.009−6.680], p<0.001, FAERS-Japan, 1.834 [1.091−3.063], p=0.009, and JADER, 1.628 [1.039−2.551], p=0.034). Furthermore, FAERS reports confirmed that females with body weight <50kg, reports from Japan, concomitant use of drugs suppressing vitamin B_{12}, and previous platinum treatment history were positive signals of olaparib-related anemia. FAERS-Japan also showed that body weight <50kg and previous platinum treatment history were positive signals for the anemia occurrence.

Conclusion: High DPBW poses a significant risk of anemia. The co-administration of drugs suppressing vitamin B_{12} and previous platinum treatment history are also important information to evaluate the risk of olaparib-related anemia.

Introduction

Olaparib is the first oral Poly-ADP ribose polymerase (PARP) inhibitor for germline breast cancer susceptibility to gene (BRCA)-mutated cancer such as ovarian cancer [1]. Olaparib inhibits PARP and is involved in several processes, including the repair of single-strand DNA breaks, genomic stability, and programmed cell death [2]. The phase trial demonstrated that the incidence of grade 3 or higher anemia was ~ 20% in patients with ovarian cancer [3].

Anemia is one of the dose-limiting toxicities of olaparib [1], which reduces the net clinical benefit and patients' quality of life. Further, the global phase trial enrolled 5% of Japanese subjects with ovarian cancer among study subjects and demonstrated that the anemia occurrence was relatively higher in Japan than in other countries (62.5% in Japan vs. 42.2% in the other countries) [4]; however, few reports have analyzed differences in the frequency and factors contributing to anemia by nationality. This study analyzed patients' background factors associated with olaparib-related anemia developed in clinical practice using adverse event report databases at post-marketing stages.

Methods

We analyzed databases from FDA Adverse Event Reporting System (FAERS) and Japanese Adverse Drug Event Report database (JADER) that were generated from post-marketing spontaneous pharmacovigilance databases. Data were extracted from FAERS and JADER between the first quarter of 2018 and the fourth quarter of 2021 in this study. FAERS includes 14,000,000 cases of adverse events reported after April 2004 worldwide [5]. JADER includes 440,000 cases of adverse events that occurred specifically in Japan after April 2004 [5]. FAERS database consists of seven data tables: patient demographic and administrative information, drug and biologic information, adverse events, patient outcomes, report sources, start end dates of drug therapy, and indications for use/diagnosis. JADER consists of four data tables: patient demographic information, drug information, adverse events, and primary disease. In JADER, age and body weight are categorized (e.g., 20s, 30s, and 40s); we converted each value to its median (e.g., 20s to 25 years old). The source of the databases complies with the guidelines set by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the databases adhere to ICH-standardized adverse event information guidelines [6]. For this analysis, adverse event reports were downloaded from FDA websites (https://www.fda.gov/, accessed on May 4th, 2022) and the Pharmaceuticals and Medical Devices Agency (http://www.pmda.go.jp/, accessed on May 4th, 2022). Further, FAERS reports were only extracted from data reported from Japan and were defined as FAERS-Japan [7]. Reports with the same case number were identified as duplicate reports and we used the most recent report as recommended by the FDA [8].

Collected data included case id, drug name, adverse event name, the start date of administration, the end date of administration, date of occurrence of adverse event, sex, age, body weight, reporting country, and daily olaparib dose, and the daily olaparib dose per body weight (DPBW) was calculated. We also collected concomitant medications known to reduce folic acid (i.e., trimethoprim/sulfamethoxazole, methotrexate, carbamazepine, oxcarbazepine, primidone, valproate, gabapentin, phenytoin, and sulphasalazine) [9–11], vitamin B_{12} levels (i.e., proton pump inhibitor, histamine 2 receptor antagonist, metformin, phenobarbital, pregabalin, primidone, and topiramate) [11–12] to clarify the association between these medications and macrocytic anemia, which is the main type of olaparib-related anemia [13]. Further, we collected strong cytochrome P450 3A4 (CYP3A4) inhibitors (i.e., clarithromycin, erythromycin, itraconazole, ketoconazole, and voriconazole), moderate CYP3A4 inhibitors (i.e., aprepitant, cimetidine, cyclosporin, fluconazole, fluvoxamine, imatinib, posaconazole, and verapamil), and CYP3A4 inducers (i.e., bosentan, carbamazepine, phenytoin, and rifampicin) [14], since olaparib is primarily metabolism via CYP3A4/5 (84% of total clearance) [15]. Although the elevated olaparib plasma exposure was observed in patients with hepatic/renal impairment [16], FAERS and JADER did not include clinical laboratory data such as serum creatinine level and alanine aminotransferase. Therefore, we defined the reports of concomitant use of phosphate binders as CKD since an increase in hyperphosphatemia (serum phosphate level ≥ 4.5 mg/dL) is notable at an eGFR of about 60 mL/min/1.73m^2 [17]. Further, we defined the reports of concomitant use of rifaximin and branched chain amino acids as severe liver disease

history [18]. Since olaparib is one of the therapeutic options available for maintenance therapy of ovarian and pancreatic cancer after platinum-based chemotherapy [19–20], a previous platinum treatment history was also collected.

Adverse Events Detection

Adverse events are coded according to preferred terms (anemia; 10002034) derived from Medical Dictionary for Regulatory Activities (MedDRA) terminology. Event reports are identified using the standardized MedDRA ver. 25.0 query. Anemia occurrence during olaparib administration was defined as 'anemia' and other adverse events were defined as 'no anemia'.

Statistical Analyses

Statistical analyses were carried out using R software version 4.1.3 (R Core Team, 2022) [21]. Statistical significance was defined as a two-tailed p-value < 0.05. Categorical and continuous variables on patients' backgrounds were summarized as median [interquartile range (IQR)] and frequency (in percentage), respectively. Signal detection was evaluated using reporting odds ratio (ROR) with 95% confidence interval (CI) using univariate logistic regression analysis, similar to previously reported results [22]. Adjusted ROR (aROR) for anemia was calculated by adjusting gender since female is more likely to develop anemia in adulthood [23–25]. The present study categorized age, body weight, and DPBW as binary variables based on the findings of previous reports and median value: age ($\geq$ 60 years or < 60 years, and $\geq$ 80 years or < 80 years), body weight ($\geq$ 50 kg or < 50 kg), and DPBW ($\geq$ 12 mg/kg or < 12 mg/kg) [26]. A statistically significant ROR was formally defined as a lower limit of the 95% CI exceeding 1.0. In anemia occurrence groups, patients' characteristics with and without anemia from Japan and the other countries were compared using Fisher's exact test.

Results

FAERS

A flow chart of report selection by FAERS is depicted in Fig. 1A. A total of 9,685 reports receiving olaparib were extracted, of which 2,981 duplicated reports were excluded from the dataset after data cleaning. The remaining 6,704 reports were subject to the following analysis. The reports attributed to the occurrence of olaparib-related anemia were 332 (5%) in FAERS. Among 6,704 reports, 1,064 (15.9%) were reported from Japan.

Patient characteristics in FAERS are listed in Table 1. There was a significant difference in characteristics with and without anemia for females (anemia, n = 312, 94% vs. no anemia, n = 4,777, 75%, p < 0.001), body weight (anemia, 51.0 [44–62] kg vs. no anemia, 64.0 [55–77.7] kg, p < 0.001), DPBW (anemia, 11.5 [8.7–13.3] mg/kg vs. no anemia, 8.1 [6–10.2] mg/kg, p < 0.001), concomitant use of drugs suppressing

vitamin B_{12} (anemia, n = 10, 3% vs. no anemia, n = 89, 1.4%, p = 0.030), and previous platinum treatment history (anemia, n = 16, 4.8% vs. no anemia, n = 76, 1.2%, p < 0.001), respectively. As for the Japanese population of FAERS, there was a significant difference between anemia and no anemia: (anemia, n = 176, 53% vs. no anemia, n = 888, 13.9%, p < 0.001), as shown in **Supplemental data 1**. Additionally, this study found a significant difference in characteristics between reports from Japan and other countries for females (Japan, n = 994, 93.4% vs. other countries, n = 4,095, 72.6%, p < 0.001), body weight (Japan, 50.0 [44−57] kg vs. other countries, 66 [56−79.8] kg, p < 0.001), DPBW (Japan, 12.5 [10.5−13.6] mg/kg vs. other countries, 9.4 [7.8−11.3] mg/kg, p < 0.001), and concomitant use of drugs suppressing vitamin B_{12} (Japan, n = 24, 2.3% vs. other countries, n = 75, 1.3%, p = 0.026), as shown in **Supplemental data 2**.

Table 1
Clinical characteristics of FAERS and JADER

Variables	FAERS			JADER		
	Anemia	No anemia		Anemia	No anemia	
	N = 332	N = 6372	p–value	N = 297	N = 992	p–value
Sex						
Female, n (%)	312 (94.0)	4777 (75.0)	< 0.001	277 (93.3)	951 (95.9)	0.057
Male, n (%)	17 (5.1)	1051 (16.5)		17 (5.7)	32 (3.2)	
Unknown, n (%)	3 (0.9)	544 (8.5)		3 (1.0)	9 (0.9)	
Age, years	63.0 [54.0–71.0]	63.0 [55.0–71.0]	0.848	65.0 [55.0–75.0]	65.0 [55.0–75.0]	0.305
Unknown, n (%)	23 (6.9)	2922 (45.9)		25 (8.4)	271 (27.3)	
Body weight, kg	51.0 [44.0–62.0]	64.0 [55.0–77.7]	< 0.001	55.0 [45.0–55.0]	55.0 [45.0–57.5]	0.394
Unknown, n (%)	147 (44.3)	5243 (82.3)		155 (52.2)	752 (75.8)	
DPBW, mg/kg	11.5 [8.7–13.3]	8.1 [6.0–10.2]	< 0.001	10.9 [10.9–13.3]	10.9 [9.2–13.3]	0.041
Suppressing folic acid, n (%)	1 (0.3)	15 (0.2)	0.557	0 (0.0)	0 (0.0)	1.000
Suppressing vitamin B_{12}, n (%)	10 (3.0)	89 (1.4)	0.030	5 (1.7)	18 (1.8)	1.000
Strong CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000	1 (0.3)	0 (0.0)	1.000
Moderate CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000	1 (0.3)	2 (0.2)	0.545

CKD, chronic kidney disease; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System;

JADER, Japanese Adverse Drug Event Report database

Data are shown as frequency (in percentage) or median [interquartile range].

Variables	FAERS			JADER		
	Anemia	No anemia		Anemia	No anemia	
	N = 332	N = 6372	p−value	N = 297	N = 992	p−value
CYP3A4 inducers, n (%)	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
Previous platinum treatment history, n (%)	16 (4.8)	76 (1.2)	< 0.001	6 (2.0)	19 (1.9)	1.000
CKD, n (%)	1 (0.3)	8 (0.1)	0.367	0 (0.0)	0 (0.0)	1.000
Liver disorder, n (%)	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
CKD, chronic kidney disease; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System;						
JADER, Japanese Adverse Drug Event Report database						
Data are shown as frequency (in percentage) or median [interquartile range].						

A summary of the occurrence of olaparib-related anemia risk in FAERS is shown in Table 2. Body weight < 50kg (aROR; 4.417 [95% CI: 3.148−6.198], p < 0.001), reports from Japan (aROR; 5.932 [95% CI: 4.704−7.480], p < 0.001), DPBW ≥ 12 mg/kg (aROR; 4.483 [95% CI: 3.009−6.680], p < 0.001), concomitant use of drugs suppressing vitamin B_{12}, (aROR; 2.279 [95% CI: 1.166−4.456], p = 0.016), and previous platinum treatment history (aROR; 3.822 [95% CI: 2.188−6.675], p < 0.001) were significant signal with the occurrence of olaparib-related anemia. In FAERS data, proton pump inhibitor, histamine 2 receptor antagonist, and anti-epileptic drugs were concomitantly received as drugs suppressing vitamin B_{12}; proton pump inhibitor or histamine 2 receptor antagonist accounted for anemia 6 (1.5%) and no anemia 72 (1.1%), anti-epileptic drugs accounted for anemia 4 (1.2%) and no anemia 8 (0.1%), respectively. There were no patients receiving metformin and pregabalin.

Table 2
Risk analyses of olaparib-related anemia by FAERS and JADER

	FAERS				JADER			
	ROR [95% CI]	p–value	aROR [95% CI]	p–value	ROR [95% CI]	p–value	aROR [95% CI]	p–value
Female	4.038 [2.467–6.609]	< 0.001			0.548 [0.300–1.002]	0.057		
≥ 60 years	0.964 [0.759–1.224]	0.764	1.096 [0.861–1.397]	0.456	1.030 [0.776–1.367]	0.840	1.030 [0.773–1.371]	0.842
≥ 80 years	0.952 [0.606–1.496]	0.832	1.172 [0.741–1.854]	0.497	0.900 [0.482–1.679]	0.740	0.905 [0.485–1.691]	0.755
< 50kg	4.964 [3.555–6.932]	< 0.001	4.417 [3.148–6.198]	< 0.001	1.209 [0.796–1.834]	0.373	1.317 [0.861–2.013]	0.204
Reports from Japan	6.967 [5.553–8.742]	< 0.001	5.932 [4.704–7.480]	< 0.001	–	–	–	–
DPBW ≥ 12 mg/kg	5.120 [3.456–7.584]	< 0.001	4.483 [3.009–6.680]	< 0.001	1.525 [1.079–2.377]	0.042	1.628 [1.039–2.551]	0.034
Suppressing folic acid	1.280 [0.169–9.722]	0.811	1.133 [0.148–8.643]	0.904	–	–	–	–
Suppressing vitamin B_{12}	2.192 [1.130–4.255]	0.020	2.279 [1.166–4.456]	0.016	0.927 [0.341–2.517]	0.881	0.869 [0.318–2.378]	0.785
Previous platinum treatment history	4.195 [2.418–7.276]	< 0.001	3.822 [2.188–6.675]	< 0.001	1.061 [0.420–2.681]	0.901	1.091 [0.432–2.760]	0.854
CKD	2.403 [0.300–19.272]	0.409	2.994 [0.359–24.935]	0.311	-	-	-	-

aROR, adjusted reporting odds ratio; CI, confidence interval; CKD, chronic kidney disease; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System; JADER, Japanese Adverse Drug Event Report database

aROR was calculated to control for gender differences.

JADER

As shown in Fig. 1B, there were 1,699 reports in JADER. We conducted data cleaning and excluded 410 duplicated data from the original dataset; the remaining 1,289 reports were subject to the following analysis. The number of reports of anemia occurrence during the administration of olaparib was 297 (23%).

Patient characteristics in JADER are also listed in Table 1. There was a significant difference in characteristics with and without anemia for DPBW (anemia, 10.9 [10.9−13.3] mg/kg vs. no anemia, 10.9 [9.2−13.3] mg/kg, p = 0.041).

A summary of olaparib-related anemia in JADER is shown in Table 2. DPBW ≥ 12 mg/kg (aROR; 1.628 [95% CI: 1.039−2.551], p = 0.034) was significant signal with the occurrence of olaparib-related anemia.

Faers-japan

Patient characteristics in FAERS-Japan are listed in Table 3. Significant differences were observed in body weight, DPBW, and previous platinum treatment history between with and without anemia; body weight (anemia, 47 [43.0−54.0] kg vs. no anemia, 52.0 [45.0−59.3] kg, p = 0.038), DPBW (anemia, 12.4 [9.6−13.6] mg/kg vs. no anemia, 10.5 [8.8−12.8] mg/kg, p = 0.017), and previous platinum treatment history (anemia, n = 9, 5.1% vs. no anemia, n = 10, 1.1%, p = 0.002). A summary of anemia occurrence risk with olaparib in FAERS-Japan is shown in Table 4. Body weight < 50kg (aROR; 2.021 [95% CI: 1.240− 3.293], p = 0.004), DPBW ≥ 12 mg/kg (aROR; 1.834 [95% CI: 1.091−3.063], p = 0.009), and previous platinum treatment history (aROR; 4.483 [95% CI: 1.794−11.207], p = 0.001) were thus significantly associated with the anemia occurrence.

Table 3
Clinical characteristics of FAERS-Japan

Variables	FAERS-Japan		
	Anemia	No anemia	
	N = 176	N = 888	p−value
Sex			
Female, n (%)	172 (97.7)	822 (92.6)	0.255
Male, n (%)	3 (1.7)	33 (3.7)	
Unknown, n (%)	1 (0.6)	33 (3.7)	
Age, years	63.0 [55.0−72.0]	62.0 [53.0−70.0]	0.205
Unknown, n (%)	9 (5.1)	305 (34.3)	
Body weight, kg	47.0 [43.0−54.0]	52.0 [45.0−59.3]	0.038
Unknown, n (%)	63 (35.8)	724 (81.5)	
DPBW, mg/kg	12.4 [9.6−13.6]	10.5 [8.8−12.8]	0.017
Suppressing folic acid, n (%)	1 (0.6)	2 (0.2)	0.419
Suppressing vitamin B_{12}, n (%)	6 (3.4)	18 (2.0)	0.265
Strong CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000
Moderate CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000
CYP3A4 inducers, n (%)	0 (0.0)	0 (0.0)	1.000
Previous platinum treatment history, n (%)	9 (5.1)	10 (1.1)	0.002
CKD, n (%)	1 (0.6)	1 (0.1)	0.304
Liver disease, n (%)	0 (0.0)	0 (0.0)	1.000

CKD, chronic kidney disease; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System.

Data are shown as frequency (in percentage) or median [interquartile range].

Table 4
Risk of anemia occurrence risk with olaparib of FAERS-Japan

FAERS-Japan				
	ROR [95% CI]	p−value	aROR [95% CI]	p−value
Female	2.302 [0.698−7.591]	0.171		
≥ 60 years	1.060 [0.744−1.511]	0.746	1.094 [0.766−1.564]	0.621
≥ 80 years	1.556 [0.792−3.056]	0.199	1.660 [0.839−3.287]	0.146
< 50kg	2.056 [1.263−3.347]	0.004	2.021 [1.240−3.293]	0.004
DPBW ≥ 12 mg/kg	1.838 [1.103−3.063]	0.009	1.834 [1.091−3.063]	0.009
Suppressing folic acid	2.531 [0.228−28.070]	0.449	2.398 [0.216−26.592]	0.476
Suppressing vitamin B_{12}	1.706 [0.667−4.360]	0.265	1.825 [0.705−4.726]	0.215
Previous platinum treatment history	4.732 [1.894−11.821]	0.001	4.483 [1.794−11.207]	0.001
CKD	5.069 [0.316−81.419]	0.252	4.801 [0.299−77.135]	0.268
aROR, adjusted reporting odds ratio; CI, confidence interval; CKD, chronic kidney disease; DPBW, daily olaparib dose per body weight;				
FAERS, FDA Adverse Event Reporting System.				
aROR was calculated to control for gender differences.				

Discussion

Our findings suggest that high DPBW has a significant positive association with olaparib-related anemia, which was demonstrated in both the FAERS and JADER real-world databases. In addition to DPBW, FAERS reports confirmed that olaparib-related anemia is significantly associated with reports from Japan, concomitant use of drugs suppressing vitamin B_{12}, and previous platinum treatment history. A significant difference in characteristics between reports from Japan and other countries were observed for females, body weight, DPBW, and concomitant use of drugs suppressing vitamin B_{12}. Additionally, FAERS-Japan showed that previous platinum treatment history was significantly associated with the anemia occurrence.

Pharmacokinetics and pharmacodynamics analyses from the time-concentration data on the phase III study revealed an exposure-response relationship between a decline in hemoglobin (Hb) level and exposure to olaparib [27]. High olaparib exposure was reported to increase the risk of adverse events [28–29]. Generally, Japanese people tend to have relatively small body sizes [30]. Furthermore, a previous study demonstrated that underweight Japanese patients had high rates of olaparib-related adverse events such as severe nausea, lymphopenia, and neutropenia [31]. Since olaparib is administered at a fixed dose regardless of body weight, DPBW is relatively high in the population with small body size as a result. Thus, high DPBW may affect the incidence of anemia in this population. Indeed, underweight individuals are considered to have a higher risk of anemia and iron deficiency than overweight individuals in female [32–33]. In addition, it is revealed that iron deficiency anemia in Japan is higher than that in other countries [34]. Nutritional factors may be associated with the anemia occurrence, which differs between nationalities.

In this study, female was found to be a significant factor for anemia associated with olaparib in the FAERS database. Females tends to experience anemia owing to menstrual blood loss [35]; however, menstruation did not appear to be associated with anemia because the dataset included numerous study subjects at menopause. Since there were more underweight (≤ 50 kg) females than males in the FAERS database, an interaction effect between female and low body weight cannot be ruled out. Vitamin B_{12} deficiency causes macrocytic anemia, which is common in Western countries [36]. Additionally, vitamin B_{12} deficiency is also prevalent among underweight people [37]. Our findings confirmed drugs suppressing vitamin B_{12} were associated with olaparib-related anemia occurrence. Concomitant use of drugs suppressing vitamin B_{12} such as proton pump inhibitors and histamine 2 receptor antagonists block the absorption of vitamin B_{12} through an increase in gastric pH [38]. Additionally, the previous study highlighted the relationship between antiepileptic drugs and vitamin B_{12} deficiency [11]. The long-term administration of antiepileptic drugs increases homocysteine level, thus resulting in a decrease in serum vitamin B_{12} [39]. Olaparib and other drugs suppressing vitamin B_{12} may complementally deteriorate hemoglobin homeostasis, resulting in macrocytic anemia. In our study, olaparib-related anemia is significantly associated with the concomitant use of drugs suppressing vitamin B_{12} only in FAERS, but not in JADER and FAERS-Japan due to the small number of reports. Generally, it takes a long-term (e.g. more than 12 months) to develop vitamin B_{12} deficiency [11, 40]. We could not investigate the effect of various administration periods of drugs suppressing vitamin B_{12}, which is an issue to be solved in future studies.

Chemotherapy agents can cause DNA damage and olaparib impedes its repair. Therefore, olaparib give damages to blood cells alongside chemotherapeutic agents [41–44]. Carboplatin has accumulated various antiproliferative effects throughout the formation of platinum DNA adducts [45–46]. Indeed, cancers arising in BRCA mutation carriers are relatively hypersensitive to platinum-based therapies [47]. Platinum-based treatments are associated with an increased risk of anemia [48], thus supporting our findings. Additionally, bone marrow function deteriorates owing to repeated chemotherapy cycles [49].

Thus, it is necessary to pay attention to the anemia occurrence in patients with low Hb levels due to previous chemotherapy treatments.

There are several limitations of this study. First, spontaneous adverse event reports could not be collected systematically. Although we only define anemia occurrence during olaparib administration as anemia reports, the causality between events and medications is uncertain. Second, this study had incomplete laboratory data. Third, information regarding the concomitant use of drugs that potentially interact with olaparib was lacking from both FAERS and JADER. Fourth, since FAERS and JADER did not include clinical laboratory data such as serum creatinine level and alanine aminotransferase, we could not evaluate renal and liver functions as risk factors of olaparib-related amenia. Finally, the adverse events in FAERS and JADER were reported according to the MedDRA, which did not evaluate the severity of anemia events.

In conclusion, this study identified the various factors associated with olaparib-related anemia using adverse event report databases. In particular, high DPBW was identified as a significant positive signal for anemia. Furthermore, the concomitant use of drugs suppressing vitamin B_{12} and previous platinum treatment history contributed to olaparib-related anemia. Our findings should be confirmed by registry studies or through further research.

Abbreviations

aROR, adjusted reporting odds ratio; CKD, chronic kidney disease; CI, confidence interval; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System; FDA, food and drug administration; Hb, hemoglobin; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IQR, interquartile range; JADER, Japanese Adverse Drug Event Report database; MedDRA, Medical Dictionary for Regulatory Activities; PARP, Poly-ADP ribose polymerase

Declarations

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

Ethical Approval

Because we gave advance notice to PMDA in accordance to the terms of use for JADER, patient consent was not applicable.

Competing interests

All of the authors declare no conflicts of interest.

Authors' contributions

Funding

Availability of data and materials

The FAERS and JADER datasets analysed during the current study are available on FDA websites (https://www.fda.gov/) and PMDA website (https://www.pmda.go.jp/)

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Tables

Table 1. Clinical characteristics of FAERS and JADER

Variables	FAERS			JADER		
	Anemia	No anemia		Anemia	No anemia	
	N = 332	N = 6372	p−value	N = 297	N = 992	p−value
Sex						
Female, n (%)	312 (94.0)	4777 (75.0)	<0.001	277 (93.3)	951 (95.9)	0.057
Male, n (%)	17 (5.1)	1051 (16.5)		17 (5.7)	32 (3.2)	
Unknown, n (%)	3 (0.9)	544 (8.5)		3 (1.0)	9 (0.9)	
Age, years	63.0 [54.0−71.0]	63.0 [55.0−71.0]	0.848	65.0 [55.0−75.0]	65.0 [55.0−75.0]	0.305
Unknown, n (%)	23 (6.9)	2922 (45.9)		25 (8.4)	271 (27.3)	
Body weight, kg	51.0 [44.0−62.0]	64.0 [55.0−77.7]	<0.001	55.0 [45.0−55.0]	55.0 [45.0−57.5]	0.394
Unknown, n (%)	147 (44.3)	5243 (82.3)		155 (52.2)	752 (75.8)	
DPBW, mg/kg	11.5 [8.7−13.3]	8.1 [6.0−10.2]	<0.001	10.9 [10.9−13.3]	10.9 [9.2−13.3]	0.041
Suppressing folic acid, n (%)	1 (0.3)	15 (0.2)	0.557	0 (0.0)	0 (0.0)	1.000
Suppressing vitamin B_{12}, n (%)	10 (3.0)	89 (1.4)	0.030	5 (1.7)	18 (1.8)	1.000
Strong CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000	1 (0.3)	0 (0.0)	1.000
Moderate CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000	1 (0.3)	2 (0.2)	0.545
CYP3A4 inducers, n (%)	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
Previous platinum treatment history, n (%)	16 (4.8)	76 (1.2)	<0.001	6 (2.0)	19 (1.9)	1.000
CKD, n (%)	1 (0.3)	8 (0.1)	0.367	0 (0.0)	0 (0.0)	1.000
Liver disorder, n (%)	0 (0.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000

CKD, chronic kidney disease; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System;

JADER, Japanese Adverse Drug Event Report database

Data are shown as frequency (in percentage) or median [interquartile range].

Table 2. Risk analyses of olaparib-related anemia by FAERS and JADER

	FAERS				JADER			
	ROR [95% CI]	p–value	aROR [95% CI]	p–value	ROR [95% CI]	p–value	aROR [95% CI]	p–value
Female	4.038 [2.467–6.609]	<0.001			0.548 [0.300–1.002]	0.057		
≥60 years	0.964 [0.759–1.224]	0.764	1.096 [0.861–1.397]	0.456	1.030 [0.776–1.367]	0.840	1.030 [0.773–1.371]	0.842
≥80 years	0.952 [0.606–1.496]	0.832	1.172 [0.741–1.854]	0.497	0.900 [0.482–1.679]	0.740	0.905 [0.485–1.691]	0.755
<50kg	4.964 [3.555–6.932]	<0.001	4.417 [3.148–6.198]	<0.001	1.209 [0.796–1.834]	0.373	1.317 [0.861–2.013]	0.204
Reports from Japan	6.967 [5.553–8.742]	<0.001	5.932 [4.704–7.480]	<0.001	–	–	–	–
DPBW ≥12 mg/kg	5.120 [3.456–7.584]	<0.001	4.483 [3.009–6.680]	<0.001	1.525 [1.079–2.377]	0.042	1.628 [1.039–2.551]	0.034
Suppressing folic acid	1.280 [0.169–9.722]	0.811	1.133 [0.148–8.643]	0.904	–	–	–	–
Suppressing vitamin B_{12}	2.192 [1.130–4.255]	0.020	2.279 [1.166–4.456]	0.016	0.927 [0.341–2.517]	0.881	0.869 [0.318–2.378]	0.785
Previous platinum treatment history	4.195 [2.418–7.276]	<0.001	3.822 [2.188–6.675]	<0.001	1.061 [0.420–2.681]	0.901	1.091 [0.432–2.760]	0.854
CKD	2.403 [0.300–19.272]	0.409	2.994 [0.359–24.935]	0.311	-	-	-	-

aROR, adjusted reporting odds ratio; CI, confidence interval; CKD, chronic kidney disease; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System; JADER, Japanese Adverse Drug Event Report database aROR was calculated to control for gender differences.

Table 3. Clinical characteristics of FAERS-Japan

Variables	FAERS-Japan		
	Anemia	No anemia	
	N = 176	N = 888	p−value
Sex			
Female, n (%)	172 (97.7)	822 (92.6)	0.255
Male, n (%)	3 (1.7)	33 (3.7)	
Unknown, n (%)	1 (0.6)	33 (3.7)	
Age, years	63.0 [55.0−72.0]	62.0 [53.0−70.0]	0.205
Unknown, n (%)	9 (5.1)	305 (34.3)	
Body weight, kg	47.0 [43.0−54.0]	52.0 [45.0−59.3]	0.038
Unknown, n (%)	63 (35.8)	724 (81.5)	
DPBW, mg/kg	12.4 [9.6−13.6]	10.5 [8.8−12.8]	0.017
Suppressing folic acid, n (%)	1 (0.6)	2 (0.2)	0.419
Suppressing vitamin B_{12}, n (%)	6 (3.4)	18 (2.0)	0.265
Strong CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000
Moderate CYP3A4 inhibitor, n (%)	0 (0.0)	0 (0.0)	1.000
CYP3A4 inducers, n (%)	0 (0.0)	0 (0.0)	1.000
Previous platinum treatment history, n (%)	9 (5.1)	10 (1.1)	0.002
CKD, n (%)	1 (0.6)	1 (0.1)	0.304
Liver disease, n (%)	0 (0.0)	0 (0.0)	1.000

CKD, chronic kidney disease; CYP, cytochrome P450; DPBW, daily olaparib dose per body weight; FAERS, FDA Adverse Event Reporting System.

Data are shown as frequency (in percentage) or median [interquartile range].

**Table 4.** Risk of anemia occurrence risk with olaparib of FAERS-Japan

| | FAERS-Japan | | | |
	ROR [95% CI]	p–value	aROR [95% CI]	p–value
Female	2.302 [0.698–7.591]	0.171		
≥60 years	1.060 [0.744–1.511]	0.746	1.094 [0.766–1.564]	0.621
≥80 years	1.556 [0.792–3.056]	0.199	1.660 [0.839–3.287]	0.146
<50kg	2.056 [1.263–3.347]	0.004	2.021 [1.240–3.293]	0.004
DPBW ≥12 mg/kg	1.838 [1.103–3.063]	0.009	1.834 [1.091–3.063]	0.009
Suppressing folic acid	2.531 [0.228–28.070]	0.449	2.398 [0.216–26.592]	0.476
Suppressing vitamin B_{12}	1.706 [0.667–4.360]	0.265	1.825 [0.705–4.726]	0.215
Previous platinum treatment history	4.732 [1.894–11.821]	0.001	4.483 [1.794–11.207]	0.001
CKD	5.069 [0.316–81.419]	0.252	4.801 [0.299–77.135]	0.268

aROR, adjusted reporting odds ratio; CI, confidence interval; CKD, chronic kidney disease; DPBW, daily olaparib dose per body weight;
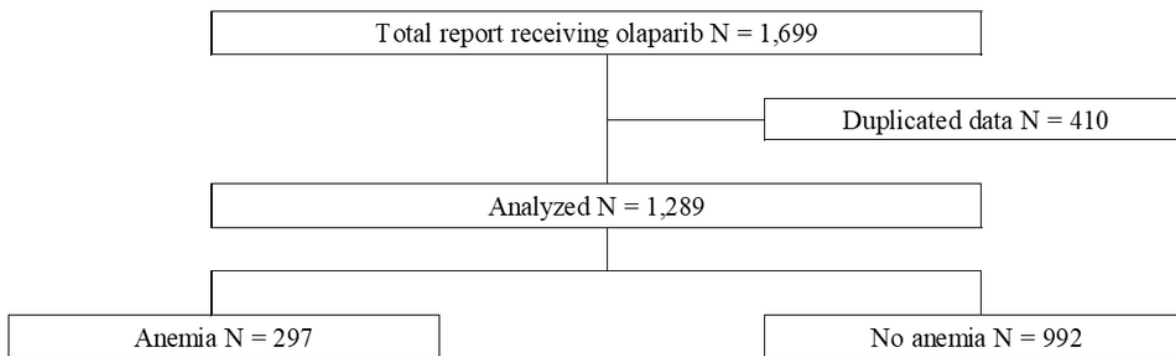
FAERS, FDA Adverse Event Reporting System.

aROR was calculated to control for gender differences.

Figures
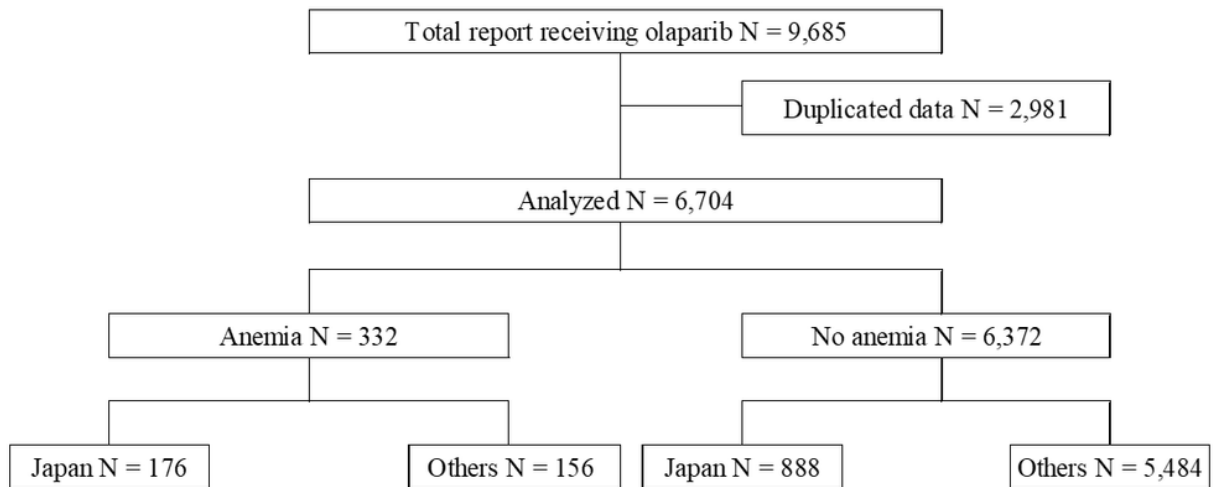
(A)

(B)

Figure 1

A Flow chart of FDA Adverse Event Reporting System (FAERS)

B Flow chart of Japanese Adverse Drug Event Report database (JADER)

Supplementary Files

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