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CORRESPONDENCE

Poly(ADP-ribose) polymerase inhibitor-associated myelodysplastic syndrome/acute myeloid leukemia: a pharmacovigilance analysis of the FAERS database

The US Food and Drug Administration (FDA) warned that poly(ADP-ribose) polymerase (PARP) inhibitors may induce myelodysplastic syndromes (MDSs) and acute myeloid leukemia (AML) in the label. The supporting data were mostly from clinical trials with a low incidence of 0.5%-1.4%.[1] However, the evidence in real world was still limited. To further access the risk of PARP inhibitors causing MDS/AML, we conducted a pharmacovigilance disproportionality analysis of the FDA Adverse Event Reporting System (FAERS) database from 2014 quarter (Q) 4 to 2020 Q1.

The PARP inhibitors in the study included olaparib, niraparib, rucaparib, and talazoparib. We selected bevacizumab as a comparator drug during the same period. We used generic names and brand names to identify drugs and preferred terms of Medical Dictionary for Regulatory Activities (MedDRA version 23.0) to identify MDS/AML cases. Reporting odds ratio (ROR) was used to calculate disproportionality. If there were at least three cases and the lower limit of the 95% confidence interval (CI) exceeded 1, it was defined as a significant signal. The larger ROR value meant the stronger signal.

A total of 319 cases of PARP inhibitor-associated MDS/AML were identified (Table 1). The number of PARP inhibitor-related MDS/AML reports increased dramatically from 2015 to 2019 (2 cases in 2015 and 115 cases in 2019). The majority of cases originated from Europe (59.87%) and America (31.66%). Patients with PARP inhibitor-related MDS/AML were mostly women ($n = 292$, 91.54%) with ovarian cancer ($n = 251$, 78.68%). The median [interquartile range (IQR)] age was 64 (58-70) years and there was little difference in the number of patients over 65 ($n = 112$, 35.11%) and under 65 ($n = 114$, 35.74%). The median (IQR) time to event onset was 449 (222-654) days. Olaparib, the first PARP inhibitor on the market, was associated with most cases ($n = 251$, 78.68%). Talazoparib-related MDS/AML had not been reported yet. Compared with the full database, treatment with PARP inhibitors was associated with higher reporting of MDS/AML (ROR 16.47, 95% CI 14.72-18.44). The ROR (95% CI) for olaparib, niraparib, and rucaparib was 48.03 (42.21-54.64), 6.58 (5.03-8.61), and 2.23 (1.32, 3.77), respectively. Furthermore, an MDS/AML signal was detected for PARP inhibitors compared with bevacizumab (ROR 4.58, 95% CI 3.81, 5.52).

Certain alkylating agents, topoisomerase II inhibitors, and platinum compounds[2] have been reported to increase the risk of MDS/AML more than fivefold. Some patients receiving bevacizumab after initial chemotherapy develop MDS/AML.[3] MDS/AML has been considered to be a consequence of DNA damage.[4] The mechanism of PARP inhibitors associated with MDS/AML remains unclear, which may be due to long-time exposure to DNA damage. PARP inhibitors restrain DNA repair and induce cancer cell death by inhibiting PARP.[5]

Table 1. Characteristics of patients with MDS/AML associated with PARP inhibitors

Characteristics		Reports, *n* (%)[a]
Gender		
	Female	292 (91.54)
	Male	14 (4.39)
	Missing	13 (4.07)
Age at onset		
	<65 years	114 (35.74)
	≥65 years	112 (35.11)
	Missing	93 (29.15)
Reporting year		
	2014[b]	0 (0)
	2015	2 (0.63)
	2016	21 (6.58)
	2017	53 (16.61)
	2018	87 (27.27)
	2019	115 (36.05)
	2020[c]	41 (12.86)
Region		
	Europe	191 (59.87)
	America	101 (31.66)
	Asia	19 (5.96)
	Oceania	8 (2.51)
	Africa	0 (0)
Indications		
	Ovarian cancer	242 (75.86)
	Breast cancer	8 (2.51)
	Fallopian tube cancer	5 (1.57)
	Prostate cancer	11 (3.44)
	Other cancers	14 (4.39)
	Missing	39 (12.23)
Outcome		
	Death	101 (31.66)
	Life-threatening	56 (17.55)
	Disability	1 (0.31)
	Hospitalization	50 (15.67)
	Other serious	109 (34.17)
	Missing	2 (0.64)
Reporter		
	Consumer	43 (13.48)
	Physician	169 (52.98)
	Pharmacist	29 (9.09)
	Other health professional	56 (17.55)
	Missing	22 (6.90)
Time to onset		
	≤1 month	6 (1.88)
	1 month to 6 months	20 (6.27)
	6 months to 1 year	27 (8.46)
	1 year to 2 years	41 (12.85)
	2 to 3 years	21 (6.58)
	>3 years	9 (2.82)
	Missing	195 (61.13)
Regimen		
	Olaparib	251 (78.68)
	Niraparib	54 (16.93)
	Rucaparib	14 (4.39)
	Talazoparib	0 (0)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PARP, poly(ADP-ribose) polymerase.
[a] Proportion of total population.
[b] From 2014 Q4.
[c] Up to 2020 Q1.

To our knowledge, this is the first pharmacovigilance analysis of MDS/AML associated with PARP inhibitors. Our study suggests a possible relationship between PARP inhibitors and MDS/AML in real world. Several limitations need to be recognized. FAERS is a spontaneous reporting system with a reporting bias and lots of missing data and the data cannot be used to calculate the incidence. Therefore, further study is still needed.

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DISCLOSURE

The authors have declared no conflicts of interest.

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