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SHORT REPORT

Clinical presentation, diagnosis and management of therapy-related hematological disorders in women with epithelial ovarian cancer treated with chemotherapy and poly-ADP-ribose polymerase inhibitors: A single-center experience

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Abstract

We investigated the occurrence and management of therapy-related hematological disorders (tr-HDs) in women with epithelial ovarian cancer (EOC) exposed to poly-ADP-ribose polymerase inhibitors (PARPi), after previous chemotherapy. We analyzed 130 consecutive EOC patients treated with PARPi at the European Institute of Oncology, Milan. In line with the literature, overall survival of the entire population was 37% at 5.5 years (89% were advanced stages). Cell blood counts were collected prior to start PARPi, at each new cycle and at monthly intervals. Patients displaying persistent and/or marked hematological abnormalities underwent bone marrow evaluation, with cytogenetic and molecular analysis. Nine patients (6,9%) developed tr-HDs, after a median 22.8 months of PARPi exposure. Two patients died early and could not be treated. Two patients have no indication for active treatment and are presently under close hematological monitoring. Five patients underwent chemotherapy followed, in three cases, by allogeneic hematopoietic transplantation: three patients are in complete remission of their hematological and gynecological malignancies at 13, 19, and 25 months; the remaining two patients died due to progression of their hematological disease. We show the potential risk of hematological disorders in EOC patients treated with chemotherapy and prolonged PARPi therapy. In our series, tr-HDs incidence was higher compared to recent reports in large series. Our observations suggest careful monitoring in order to conclusively define, on large series and prolonged follow-up, the actual risk of tr-HDs in patients under PARPi. Notably, prompt diagnosis of hematological abnormalities and appropriate management allow

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloblastic leukemia; BM, bone marrow; CBCs, cell blood counts; CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; CR, complete response; CTCAE, common terminology criteria for adverse events; DSBs, DNA double strand breaks; EB, excess of blasts; ELN, European Leukemia Network; EOC, epithelial ovarian cancer; FISH, fluorescence in situ hybridization; HRR, homologous recombination repair; IEO, European Institute of Oncology; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplasia syndrome; MDS-U, MDS unclassifiable; PARP, poly-ADP-ribose polymerase; PARPi, PARP-inhibitors; PB, peripheral blood; PR, partial response; tr-HDs, therapy-related hematological disorders; tr-MNs, therapy-related myeloid neoplasms.

achievement of remission from severe hematological complications, at least in most patients.

KEYWORDS

clinical management, epithelial ovarian cancer, hematological monitoring, PARP-inhibitors, therapy-related hematological disorders

1 | INTRODUCTION

Epithelial ovarian cancer (EOC) is the fifth most common cancer among women, the most fatal among gynecological malignancies[1] and commonly diagnosed at an advanced stage.[2] Debulking surgery followed by platinum-based chemotherapy remains the gold standard treatment.[3] However, most patients relapse[2] and most studies focused on improving rescue for recurrent disease and finding a strategy of effective maintenance therapy to delay subsequent progression. In the past few years, the poly-ADP-ribose polymerase inhibitors (PARPi) have been developed as novel and effective anticancer therapies, especially in breast cancer gene (*BRCA1*/*BRCA2*) mutation carriers. Several clinical trials have shown efficacy of PARPi in EOC, with significant improvements in progression-free survival in the recurrent setting. The benefit was demonstrated in both *BRCA*-mutated (SOLO2 trial) and *BRCA* wild-type patients (OV16/NOVA, ARIEL3 trial).[4-6] More recently, SOLO1 trial demonstrated that olaparib maintenance therapy reduced the risk of disease progression or death by 70% in patients with newly diagnosed *BRCA*-mutated EOC.[7] These studies have opened a new era in the management of EOC with approval of PARPi maintenance therapy and multiple PARPi are currently under evaluation in clinical trials.[8,9]

PARPi exert their anticancerous activity through the so-called "synthetic lethality" mechanism, which takes place when two non-lethal defects combine and result in a lethal phenotype.[10] Several cancer cells, including *BRCA*-mutated cells, are defective in their capacity to repair DNA double-strand breaks (DSBs) via the homologous recombination repair (HRR) pathway. These cancer cells have increased dependence on PARP to repair their DNA and to divide. For these defective cells, PARPi may be lethal by triggering "synthetic lethality."

Normal cells, proficient in HRR, are able to survive under PARP inhibition. Nevertheless, also normal cells, particularly those rapidly dividing, such as hematopoietic cells, might be affected by perturbations in DNA repair processes. Indeed, hematologic toxicities have been reported as frequent adverse events under PARPi therapy. A recent meta-analysis showed that the incidence of grade 3 or 4 neutropenia, thrombocytopenia and anemia in patients receiving PARPi were 32.9%, 15.9% and 9.1%, respectively.[11] These side effects frequently occur during the first months of therapy and are usually managed with temporary treatment interruptions, dose delays or reductions. Less is known on late hematologic toxicities. Regular monitoring of blood tests is recommended, with additional investigations, if hematological toxicities do not resolve after drug interruption.[12-14]

What's new?

Hematological toxicities frequently occur during the first months of therapy with PARP-inhibitors (PARPi) and are usually managed with temporary treatment interruptions. Less is known on late hematological toxicities. In this retrospective study, the authors investigated therapy-related hematological disorders in women with epithelial ovarian cancer (EOC) exposed to PARPi, after previous chemotherapy. They observed an incidence of therapy-related hematological disorders after prolonged exposure to PARPi that was considerably higher than that reported in the literature. However, the results showed that early diagnosis and prompt treatment of therapy-related hematological disorders can lead to disease remission of both hematological disorders and gynecological malignancies.

In order to evaluate PARPi long-term hematological complications, we performed a retrospective analysis on patients treated with PARPi at the European Institute of Oncology (IEO) of Milan. We describe the early diagnosis of therapy-related hematologic disorders (tr-HDs) and their management.

2 | MATERIALS AND METHODS

2.1 | Patient population

We analyzed 130 consecutive patients treated with PARPi for EOC, at IEO, between 2010 and 2018. Patients received PARPi inside an open clinical trial, as compassionate use or after regular approval of the drug. A few patients were part of double-blind clinical trials; however, only patients for whom unblinded procedures revealed the PARPi treatment were included in the present analysis. Patient characteristics and clinical parameters are reported in Table 1.

2.2 | PARPi treatments

Three different PARPi were delivered orally at the following dosages: (a) olaparib at 800 mg/day (capsule formulation) or 600 mg/day

TABLE 1 Main clinical features of 130 epithelial ovarian cancer patients treated with chemotherapy followed by poly-ADP-ribose polymerase inhibitors (PARPi) and those developing therapy-related hematological disorders during PARPi therapy

Characteristics	Global cohort (N = 130)	Patients with tr-HDs (N = 9)
Median age EOC diagnosis	54 (range 33-78)	48 (range 37-66)
Histology		
Serous carcinoma[a]	111 (85%)	8 (89%)
Endometrioid carcinoma	5 (4%)	0
Clear cell carcinoma	5 (4%)	0
Mixed carcinoma	4 (3%)	1 (11%)
NOS carcinoma	5 (4%)	0
Grade		
High	126 (97%)	8 (89%)
Intermediate	4 (3%)	1 (11%)
FIGO stage		
I	5 (4%)	0
II	9 (7%)	2 (22%)
III	91 (70%)	5 (56%)
IV	25 (19%)	2 (22%)
BRCA 1/2 germline status		
Mutated	62 (48%)	7 (78%)
Wild type/VUS	60 (46%)	2 (22%)
Unknown[b]	8 (6%)	0
Prior CT lines before PARPi		
1-2	46 (35%)	4 (45%)
3-4	68 (53%)	3 (33%)
≥5	16 (12%)	2 (22%)
Median age at PARPi start	59 (range 34-79)	55 (range 40-70)
Type of PARPi		
Olaparib	97 (74%)	7 (78%)
Niraparib	23 (18%)	0
Rucaparib	10 (8%)	2 (22%)
PARPi therapy		
Treatment	60 (46%)	2 (22%)
Maintenance	70 (54%)	7 (78%)
Type of prescription		
Regular approval/compassionate use	45 (35%)	3 (33%)
Clinical trial		
Open	81 (62%)	4 (45%)
Double-blind (*post unblinded*)	4 (3%)	2 (22%)
Duration of PARPi therapy		
Median (months)	7.5 (range 1-110.8)	22.8 (range 4.1-41.6)
≤ 6 months	51 (39%)	1 (11%)
7 to 17 months	52 (40%)	1 (11%)
≥18 months	27 (21%)	7 (78%)
Death		
Yes	44 (34%)	3 (33%)
No	77 (59%)	6 (67%)
Lost at follow-up	9 (7%)	0

Abbreviations: *BRCA*, breast cancer gene; CT, chemotherapy; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; PARPi, poly-ADP-ribose polymerase inhibitor; tr-HDs, therapy-related hematogical disorders; VUS, variable of uncertain significance.

[a]One is a serous peritoneal carcinoma.

[b]Patients included in a 2010 clinical trial regardless *BRCA* status and dead before performing the test.

(tablet formulation); (b) niraparib at 300 mg/day; (c) rucaparib at 1200 mg/day. All but five patients received PARPi after at least two previous chemotherapy lines. PARPi was administered as treatment in partial responders (PR) after platinum-based chemotherapy or as maintenance therapy in complete responders (CR). All but five patients received PARPi upon disease relapse. However, up to 46% patients received PARPi as treatment within international randomized trials. Among these, 68% received PARPi as monotherapy, whereas 32% in association with an antiangiogenic drug (cediranib) as part of an open randomized clinical trial for platinum-resistant EOC.[15] PARPi were administered until disease progression or unacceptable toxicity. Patients receiving PARPi for ≥18 months were defined long responders (Table 1). Treatment toxicities were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[16]

2.3 | Hematologic procedures

Peripheral blood (PB) samples were collected prior to start PARPi and at least monthly, at the beginning of every new cycle. Besides regular cell blood counts (CBCs), patients displaying persistent and/or marked hematological abnormalities underwent bone marrow (BM) evaluation consisting of morphologic, immunophenotypic, cytogenetic and fluorescence in situ hybridization (FISH) analysis. Identification of mutations or alterations of gene expression were performed using the diagnostic panel Oncomine Myeloid Research Assay. Analyses were performed using the IonReporter software, applying the last release of Myeloid workflow (ThermoFisher Scientific).

World Health Organization (WHO) 2016 Classification was used to define myelodysplastic syndrome (MDS) and acute leukemias (AL) subtypes[17]: for MDS prognostic score, we used the Revised International Prognostic Scoring System (IPSS-R)[18]; for AL, the European Leukemia Network (ELN).[19] Hematological procedures were performed according to internal institutional diagnostic and clinical guidelines.

2.4 | Statistical methods

Descriptive statistics were performed to report data related to patients' demographics, clinicopathological characteristics and treatments.

3 | RESULTS

3.1 | Clinical features of the whole cohort and of patients developing tr − HDs

The main clinical features of the 130 EOC patients treated with PARPi are shown in Table 1. Most patients presented with advanced International Federation of Gynecology and Obstetrics (FIGO) stage and serous (85%) high-grade (97%) carcinomas. Consistent with the literature data, the overall survival of the entire population was 37% at 5.5 years (range 1.1-16.2) since diagnosis.[20] Germline *BRCA1/2* mutations were present in approximately half of the patients. The majority was heavily pretreated prior to start PARPi. Nine patients of our cohort developed tr-HDs and their main clinical features reproduced those of the whole series (Table 1): 7 (78%) had an advanced EOC at diagnosis, 4 (45%) received two lines of chemotherapy before starting PARPi, 3 (33%) between three and four lines and 2 (22%) received at least five lines. Interestingly, 7 patients (78%) were *BRCA1/2* mutated compared to 48% in the whole series.

All patients developing tr-HDs received platinum and taxane therapy as first-line chemotherapy as well as platinum-based subsequent lines before PARPi. Overall, tr-HDs occurred in 7 patients under olaparib, 2 under rucaparib and none under niraparib. Except for one patient who received olaparib in association with antiangiogenic agent,[15] all received PARPi as monotherapy for a median of 22.8 months (range 4.1-41.6) with 7 (78%) that took the drug for more than 18 months (long responders). The median time between first-line chemotherapy and development of tr-HDs was 7.7 years (range 4.5-16).

3.2 | tr − HD diagnosis clinical presentation,management and responses

In all cases, persistence of hematological abnormalities was the main reason for referring patients to hematologic consultation. Six patients (67%) showed moderate though persistent cytopenia for at least 30 days despite PARPi interruption, 2 patients were referred after 15 days of PARPi withdrawal due to rapid and severe decline in platelet counts (CTCAE grade 4, <25.000/mm^3), the last patient was immediately hospitalized due to the presence of blasts in her PB on the start day of the cycle (Table 2). Overall, hematological abnormalities consistent with a diagnosis of tr-HD were detected in 9 out of 130 patients (6.9%) receiving PARPi treatments after chemotherapy.

One patient was diagnosed with clonal cytopenia of undetermined significance (CCUS) and five with MDS: four had MDS with excess of blasts (EB), three EB2 (BM blasts 10-19%) and one EB1 (BM blasts 5-9%) and were high-risk disease according to IPSS-R score, one had an MDS unclassifiable (MDS-U, IPSS-R score intermediate). Acute myeloblastic leukemia (AML) was diagnosed in two other patients (one AML-FAB M6 and one AML with myelodysplastic-related changes [MRC]), while one patient had a diagnosis of acute lymphoblastic leukemia (ALL), FAB L3. From a cytogenetic and molecular point of view, five patients showed del(5q)/−5 or del(7q)/−7, three had a complex karyotype and five carried a *TP53* mutated gene (Table 2).

After tr-HD diagnosis, all patients stopped PARPi, with the exception of the patient with CCUS.

Two patients died few days after MDS-EB2 diagnosis because of a massive brain hemorrhage and rapid EOC progression, respectively.

TABLE 2 Characteristics and management of patients with therapy-related Hematological Disorders

Pt	Tr-HD	EOC status at tr-HD diagnosis	Type and cycle of PARPi	Hematologic toxicity	Duration (days)	Karyotype analysis	FISH test	Molecular biology	Treatment	CT	PBSCT	CR Duration (months)	Relapse	Salvage CT	EOC status at last FUP	Death or alive	Cause of death
1	MDS-EB2	SD	OLAPARIB Cycle 23	T G1→3	30	46,XX	EGR1 deleted	Not done	NO	–	–	–	–	–	SD	Death	Cerebral bleed
2	MDS-EB2	PR	OLAPARIB Cycle 4	N G3 & Blasts	0 Immediate hematologic consult	45,XX,t(3;3)(q21;q26),-7	MECOM rearranged Monosomy 7	Negative	NO	–	–	–	–	–	PD	Death	EOC PD
3	CCUS	PR	RUCAPARIB Cycle 5	A G2 N G2	> 30	46,XX	Negative	TP53 mut	NO	–	–	–	–	–	PR	Alive	–
4	MDS-U	SD	OLAPARIB cycle 20	T G1→ 2	30	45,XX,-5,-6, der(17)t(17;?)(p11.2;?), +mar	Negative	TP53 mut ASXL1 mut	NO	–	–	–	–	–	SD	Alive	–
5	AML- MRC	SD	RUCAPARIB Cycle 26	N G2→4 T G1→2	30	46,XX,del(13)(q12q14)	D7S486 deleted	TP53 mut	YES	ICE→CR	YES	32	NO	–	CR	Alive	–
6	MDS-EB2	NED	OLAPARIB Cycle 41	N G3	30	46,XX,del(5)(q12q33),+13, −16,del(17)(p12pter)	EGR1 deleted D7S486 deleted	TP53 mut	YES	ICE→RD FLAI→ CR	YES	5	YES	Decitabine + venetoclax→ RD → phase I trial	NED	Death	Tr-HD PD
7	MDS-EB1	CR	OLAPARIB Cycle 33	T G1→2	30	44,XX, −7,del(5), t(5;18)(q11;?),del(5)(q11),-18	Not available	Not done	YES	5-aza	YES	15	NO	–	CR	Alive	
8	AML M6	SD	OLAPARIB Cycle 20	T G3→4 A G2→3	15	46,XX	Negative	TP53 mut	YES	ICE→RD FLAI→RD	NO	–	NO	Decitabine + venetoclax→ RD	PD	Death	Tr-HD PD
9	ALL L3	CR	OLAPARIB Cycle 24	T G3→4	15	46,XX,t(3;18)(p14;q22), t(8;22)(q24;q11)	MYC rearranged BCL2 deleted BCR copy gain	Negative	YES	G-MALL 2002→CR	NO	8	NO	–	CR	Alive	–

Abbreviations: A, anemia; AML M6, acute erythroblastic leukemia; ALL L3, acute lymphoblastic leukemia FAB classification; AML-MRC, acute myeloid leukemia with myelodysplastic-related changes; CCUS, clonal cytopenia undetermined significance; CT, chemotherapy; CR, complete response; EOC, epithelial ovarian cancer; FISH, fluorescence in situ hybridization; FLAI, idarubicin 12 mg/m^2 d1-d3-d5 + fludarabine 30 mg/m^2 d1-5 + cytarabine 2000 mg/m^2 d1-5 + GCSF from d0; FUP, follow-up; G, grade according to CTCAE[16]; G-MALL 2002, GMALL B-ALL/NHL 2002 Protocol[19]; ICE, idarubicin 12 mg/m^2 d1-d3 + cytarabine 100 mg/m^2 d1-7 + etoposide 100 mg/m^2 d1-5; MDS-EB1, myelodysplastic syndrome with excess blasts type 1; MDS-EB2, myelodysplastic syndrome with excess blasts type 2; MDS-U, myelodysplastic syndrome unclassifiable; mut, mutation; N, neutropenia; NED, no evidence of disease; PD, progressive disease; PR, partial response; PARPi, poly-ADP-ribose polymerase inhibitors; PBSCT, peripheral blood stem cell transplantation; RD, refractory disease; SD, stable disease; T, thrombocytopenia; 5-aza, 5-azacytidine 75 mg/m^2 d1-7 q28 for 5 cycles; Tr-HD, therapy-related hematological disorder.

TABLE 3 Characteristics of patients undergoing allogeneic hematopoietic stem cell transplantation

Pt	Tr-HD	HD status before PBMSC	EOC status	MAC/ RIC	Conditioning regimen	Source of SC	HLA compatibility	GvHD prophylaxis	Number of CD34+ cells infused/kg	Graft failure	Acute GvHD	Chronic GvHD	HD best response	EOC best response
5	AML MRC	CR	SD[a]	MAC	TREO-FLU[b]	PBSC	HLA IDENTICAL	MTX + CSA[c]	5.3×10^6	NO	YES	YES	CR	CR
6	MDS-EB2	CR	NED	MAC	TREO-FLU[b]	PBSC	HLA HAPLOIDENTICAL	CTX POST REINFUSION + MMF + TAC[d]	4.4×10^6	NO	NO	NO	CR	NED
7	MDS-EB1	CR	CR	MAC	THIO-FLU-BUSULFAN[e]	PBSC	HLA HAPLOIDENTICAL	CTX POST REINFUSION + MMF + CSA[d]	3.9×10^6	NO	NO	YES	CR	CR

Abbreviations: AML-MRC, acute myeloid leukemia with dysplastic-related changes; CR, complete response; EOC, epithelial ovarian cancer; GVHD, graft vs host disease; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MDS-EB1, myelodysplastic syndrome with excess blasts type 1; NED, no evidence of disease; MDS-EB2, myelodysplastic syndrome with excess blasts type 2; PBSCT, peripheral blood stem cell transplantation; RIC, reduced intensity conditioning; SC, stem cell; Tr-HD, therapy-related hematological disorder; SD, stable disease.

[a]Left pararectal lesion (30 mm) and peritoneal node (4 mm) stable.

[b]Treosulfan 14 g/mq day (−6; −5; −4)−fludarabine 30 mg/mq day (−6; −5; −4; −3; −2).

[c]Methotrexate 15 g/kg day +1−methotrexate 10 mg/kg day (+3; +6)−cyclosporine from day −1 to day +100 (range 150-300 mg).

[d]Cyclophosphamide 50 mg/kg day (+3; +4)−mycophenolate 15 mg/kg t.i.d. up to day+35 + tacrolimus from day +5 to day+100 (target tacrolimus level 5-15 ng/mL) or cyclosporine from day −1 to day +100 (range 150-300 mg).

[e]Thiotepa 5 mg/kg day(−7; −6)−fludarabine 50 mg/mq day (−5; −4; −3)−busulfan 3.2 mg/kg day (−5; −4; −3).

The patients with CCUS and with MDS-U have normal CBCs, are asymptomatic and with an excellent control of EOC and, therefore, they are currently on strict hematological monitoring. The remaining five patients underwent chemotherapy followed, in three of them, by allogeneic hematopoietic stem cell transplantation (allo-HSCT; Table 2).

Table 3 reports the main clinical data of the three patients undergoing allo-HSCT. In details, the patient with AML-MRC, after obtaining CR underwent a myeloablative allo-HSCT from her HLA-identical sister. Two years nine months post-allo-HSCT, she is in continuous CR. Interestingly, this patient was in PR for her EOC and she is now in CR. The patient with primary refractory MDS-EB2 achieved CR after salvage chemotherapy with FLAI regimen and underwent haploidentical allo-HSCT from her daughter. Five months posttransplant, she relapsed and died for leukemia progression, without evidence of EOC. The patient with MDS-EB1 received five cycles of 5-azacytidine obtaining CR and underwent a myeloablative haploidentical allo-HSCT from her brother, at another Center. After 16 months, she is in CR of both her hematological disease and EOC.

The remaining two patients received intensive chemotherapy without allo-HSCT. One patient with erythroblastic leukemia was refractory to various chemotherapy attempts and died for leukemia progression. The patient with ALL FAB-L3 was treated with sequential high-dose chemotherapy (GMALL B-ALL/NHL 2002 Protocol)[21] obtaining CR. Eight months after, she is in CR of both her leukemia and EOC.

Overall, at a median observation of 40 months (range 8-69.4), five out of nine patients diagnosed with post-PARPi tr-HD are alive: three after intensive treatments and two under careful clinical monitoring without need of any treatment, so far. The remaining four patients had a rapid and fatal outcome at a median of 4.9 months (range 2.6-15.2) post-PARPi tr-HD diagnosis.

4 | DISCUSSION

Our report describes the occurrence of tr-HDs in a series of 130 women with EOC receiving PARPi after chemotherapy treatments. Overall, nine patients developed tr-HDs after a median exposure time to PARPi of about 2 years. Two patients died early, while 5 patients underwent chemotherapy followed, in three cases, by allo-HSCT: 3 patients are in CR of both their hematological and gynecological malignancies at 13, 19 and 25 months since treatment completion; 2 patients, with MDS-U and CCUS, have no indication for active treatment and are presently under close hematological monitoring.

Therapy-related myeloid neoplasms secondary to alkylating agents have a long latency period (5 years on average), usually arise as MDS, which often progress rapidly to AML with MRC, very poor prognosis and median life expectancy of ~8 months. The use of prompt and intensive treatments along with allo-HSCT improved the prognostic expectancy with CR achievement at least in a subset of patients. Indeed, careful hematological monitoring is advisable in patients

displaying CBCs abnormalities under PARPi after previous exposure to chemotherapy.

In our series, all but two patients displayed the cytogenetic features most commonly observed in tr-MNs secondary to alkylating agents, as recently described.[22] Indeed, we documented chromosome 5 (del(5q)) and/or loss of either part or all chromosome 7 (del(7q) or −7), complex karyotypes and *TP53* mutations. Both PARP1 and p53, shown to directly interact, have the ability to bind DNA broken ends, acting as potential sensors and signaling molecules for the detection of DSBs. It has been shown that after increased PARP1-dependent poly(ADP-ribosyl)ation, P53 mutants actually bind with enhanced efficiency to broken DNA ends.[23] Considering the tight interplay between these two proteins, it is reasonable to believe that they are crucial for the maintenance of genomic stability and, hence, that PARP inhibition in *TP53* mutated hematopoietic cells, as in our clinical context, may contribute to leukemogenesis. However, it is difficult to discriminate the role of combination of PARPi with previous treatments in the development of cytogenetic abnormalities leading to development of tr-HDs. In fact, all nine patients developing tr-HDs received extensive chemotherapy preceding PARPi, with five of them having received three or more previous lines of chemotherapy.

Therapy-related hematological disorders incidence after treatment with PARPi vary between 1.1% and 1.5%: 1.5% with olaparib, 1.4% with niraparib and 1.1% with rucaparib.[12-14] However, data on incidence, management and long-term survival rates are limited. In our small series, the tr-HDs incidence rate of 6.9% after olaparib and rucaparib (7% and 20% of treated patients, respectively) is definitely higher compared to the one observed so far in large patient populations. Intriguingly, despite equally heavy pretreatment, no tr-HDs were observed after niraparib, although all three PARP inhibitors exhibit highly similar hematological toxicity. However, the numbers of our cohort are too small to infer differences in the leukemogenic potential of the different PARPi. Proper prospective studies are needed to answer this question. We do not know to what extent platinum-based chemotherapy, other chemotherapeutic drugs or their combination with PARPi contributed to the development of tr-HDs. In fact, we have not been able to assess whether the cytogenetic alterations and genetic variants were already present before starting PARPi treatment. We only know that CBCs were sufficiently adequate to start the treatment. Thus, the present report urges additional studies to define the real risk of tr-HDs development in patients with prolonged PARPi therapy and previous chemotherapy exposure.

Importantly, all but one patient were *BRCA1/2* mutated (89% vs 50% in the global population) as well as heavily pretreated and, therefore, likely carriers of complex mutational landscapes with potential simultaneous targeting of multiple DNA repair pathways. In this setting, PARPi may be harmful by triggering, through "synthetic lethality" mechanisms, leukemic transformation.

The average time to PARPi exposure in patients developing tr-HDs was more than three times longer compared to the duration to PARPi exposure in the whole population (22.8 vs 7.5 months, respectively). This suggests that tr-HDs development might represent a late complication in patients lengthily treated with drugs interfering in DNA repair mechanisms. This is of particular concern with the PARPi currently in use, which lack selectivity and result in simultaneous inhibition of several PARP isoforms. Indeed, sustained inhibition of PARP in *PARP-1/PARP-2* double-deficient mice results in impaired T-cell homeostasis and immune response, accumulation of spontaneous DNA damage in T-cells and development of lymphomas with long latency.[24] This might explain our finding of tr-HDs occurrence after prolonged PARPi exposure.

Despite increasing use of PARPi for treatment of a variety of cancers, no biological factors that might favor the development of hematological abnormalities in patients under PARPi therapy have been described. Clonal hematopoiesis of indeterminate potential (CHIP) is associated with an increased risk of developing blood cancer, in particular MDS/AML, and it likely represents a precancerous clonal expansion with a high potential to progress to malignant hematological diseases.[25] Currently, there are no published data addressing the relationship between DNA damaging agents, such as PARPi, and CHIP. In this view, we recently launched at our center a prospective biological study in order to identify possible genetic abnormalities associated with an increased risk for the development of tr-HDs after treatment with PARPi, including analysis of mutations in genes involved in CHIP. This might offer some new tools to stratify patients based on their risk and to perform genetic counseling, aimed to the proper assessment of both efficacy and potential side effects of PARPi therapy.

In summary, our study indicates the potential risk of severe hematological toxicity in EOC patients treated with chemotherapy and subsequently exposed to prolonged PARPi therapy. These patients need careful hematological monitoring. The management of tr-HDs in patients under PARPi is quite complex. However, prompt and adequate treatment can lead to disease remission of both hematological and gynecological malignancies.

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CONFLICT OF INTEREST

E. Todisco reports personal fees from AbbVie and Janssen, outside the submitted work. N. Colombo reports personal fees from Roche, AstraZeneca, MSD, Clovis, GSK, Novartis, Amgen, Immunogen and Pfizer outside the submitted work. C. Tarella reports personal fees from ADC Therapeutics and research support from ADC Therapeutics and TG Therapeutics outside the submitted work. All other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are all included in the current manuscript. Data sets that are minimally required to replicate the outcomes of the study will be made available upon reasonable request.

ETHICS STATEMENT

The study was authorized by the Clinical Trial Office of IEO (UID 2368). All patients gave written informed consent to their participation to the diagnostic and treatment program, according to the IEO ethical committee approval.

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