



# Hematological disorders after salvage PARPi treatment for ovarian cancer: Cytogenetic and molecular defects and clinical outcomes

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## Abstract

Inhibitors of poly(ADP-ribose) polymerase (PARPi) are increasingly employed as salvage therapy in epithelial ovarian cancer (EOC), but cytotoxic drug exposure along with PARP inhibition may favor development of hematological disorders. In our study, of 182 women with EOC treated with PARPi, 16 (8.7%) developed therapy-related myeloid neoplasms (t-MNs), with 12 cases of myelodysplasia and 4 of acute myeloid leukemia. All experienced persistent cytopenia after PARPi discontinuation. Seven patients had del(5q)/-5 and/or del(7q)/-7, nine had a complex karyotype and *TP53* mutations, recently reported as risk factor for t-MNs in EOC post-PARPi, were found in 12 out of 13 tested patients. Four patients had a rapid and fatal outcome, one had stable disease, eleven underwent induction therapy, followed by allogeneic hematopoietic cell transplantation in seven. Three of these 11 patients experienced refractory disease, and 8 had complete remission. During a 6.8 months (range 2.3-49) median observation time, 3 out of 16 patients were alive, with one surviving patient free of both solid and hematological tumors. Ten patients died because of leukemia, two because of transplant-related events, one from heart failure. Five more patients experienced persistent cell blood count abnormalities following PARPi discontinuation, without reaching MDS diagnostic criteria. A customized Myelo-panel showed clonal hematopoiesis in all five patients. These findings confirm the actual risk of

**Abbreviations:** AL, acute leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloblastic leukemia; BM, bone marrow; CBCs, cell blood counts; CCAUS, clonal cytogenetic abnormalities of undetermined significance; CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate (clinical) potential; CR, complete response; cyCR, cytogenetic CR; EB, excess of blasts; EOC, epithelial ovarian cancer; FISH, fluorescent in situ hybridization; GVHD, graft-vs-host disease; HGSO, high-grade serous ovarian carcinoma; HR, homologous recombination; ICE, idarubicin-etoposide-cytarabine; ICUS, idiopathic cytopenia of undetermined significance; IDUS, idiopathic dysplasia of unknown significance; IEO, European Institute of Oncology; IPSS-R, revised international prognostic scoring system; mCR, morphological CR; MDS, myelodysplasia; MLD, multilineage dysplasia; NGS, next generations sequencing; PARP, Poly-ADP-Ribose polymerase; PARPi, PARP-inhibitors; PB, peripheral blood; PDL, posttransplant lymphoproliferative disorder; SNP, single nucleotide polymorphisms; t-MNs, therapy-related myeloid neoplasms; VUS, variants of uncertain significance; WHO, World Health Organization.

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t-MNs in EOC patients after chemotherapy and prolonged PARPi therapy. The management of these patients is complex and outcomes are extremely poor. Careful diagnostic procedures are strongly recommended whenever unusual cytopenias develop in patients receiving PARPi therapy.

#### KEYWORDS

epithelial ovarian cancer, mutations, next generation sequencing, PARP-inhibitors, therapy-related myeloid neoplasms

#### What's new?

PARP inhibitors are increasingly used as salvage therapy in epithelial ovarian cancer. However, cytotoxic drug exposure along with PARP inhibition may favor the development of hematological disorders. Our study of 182 epithelial ovarian cancer patients confirms that the risk of secondary myeloid neoplasms after chemotherapy and prolonged PARPi cannot be minimized, with an incidence reaching 8.7%. Moreover, the authors show that management of these patients is complex, with poor outcomes despite intensive treatment regimens, likely due to the genetic complexity of the myeloid neoplasms. They recommend careful diagnostic procedures whenever unusual cytopenias develop in patients receiving PARPi.

## 1 | INTRODUCTION

Recent insights into the molecular and genetic characteristics of high-grade serous ovarian carcinoma (HGSOC) have allowed for the development of novel targeted therapeutic strategies. In particular, around 50% of all HGSOC are characterized by a deficiency in homologous recombination (HR) DNA repair.<sup>1</sup> This defect is generally due to *BRCA1/2* mutations. In some cases, genomic alterations and/or epigenetic silencing of other genes involved in the pathway, including *ATR*, *ATM*, *RAD51/54*, *CHK1/2*, *NBS1*, *PTEN* and *PALB2*,<sup>1-4</sup> may confer a so-called “BRCAness” profile, in which affected cells cannot correctly repair DNA double-strand breaks, similarly to a BRCA deficiency. The family of poly(ADP-ribose) polymerases (PARPs) is involved in single-strand break repair, and their inhibition under conditions of HR repair deficiency can be leveraged to force double-strand break lethality in cancer cells.<sup>1,5-7</sup> The molecular characteristics of HGSOC have led to the use of PARP inhibitors (PARPi) for this purpose, which have shown efficacy against epithelial ovarian cancer (EOCs) in several clinical trials with significant survival improvements when used as frontline therapy or for recurrence.<sup>8</sup>

PARP inhibitors effects in inhibiting cellular DNA repair, however, extend to normal cells, particularly those undergoing rapid cell division, such as hematopoietic cells,<sup>9</sup> and hematologic toxicities have been reported under PARPi therapy. One meta-analysis showed incidences of 32.9% for grade 3 or 4 neutropenia, 15.9% for thrombocytopenia and 9.1% for anemia in patients receiving PARPi.<sup>10</sup> These side effects frequently arise during the first months of therapy and are usually managed with temporary treatment interruptions or dose delay or reduction.

Preliminary data on the use of PARPi in recurrent disease indicate an incidence of hematologic disorders of 1% to 2%.<sup>11,12</sup> A recent meta-analysis, based on 18 randomized clinical trials, showed that PARPi significantly increased the risk of myelodysplastic syndrome (MDS) and

acute myeloid leukemia (AML) compared to placebo treatment.<sup>8</sup> Of note, this meta-analysis included trials carried out both in frontline and in recurrent disease. Subgroup analyses of the risk for therapy-related (tr)-MDS and AML with PARPi yielded odds ratios of 1.93 (0.68-5.49) with front-line maintenance and 4.79 (1.11-20.63) with second line and beyond compared to controls.<sup>8</sup> These data suggest that hematologic disorders related to therapy may be influenced by both previous platinum-based treatments and salvage PARPi. A double-blind, randomized, placebo-controlled phase 3 trial (SOLO2/ENGOT-Ov21) confirmed the efficacy of the PARPi olaparib in platinum-sensitive disease with *BRCA1/2* mutations. The final analysis from this trial has documented that MDS or AML occurred in 16 (8%) out of 195 patients in the olaparib group.<sup>12</sup> Similarly, 9 of 130 (6.9%) consecutive patients treated with PARPi after platinum-based chemotherapy developed tr-myeloid neoplasms (t-MNs) at a median 22.8 months of PARPi exposure, according to a preliminary analysis from the European Institute of Oncology (IEO) of Milan.<sup>9</sup> That study was extended and here we report the actual incidence of patients developing hematological disorders after salvage PARPi from a large series of EOC cases. In addition, we describe the peculiar cytogenetic and molecular characteristics and clinical outcomes of the patients who developed t-MN. Outcomes were quite poor in spite of intensive treatments that often include allogeneic hematopoietic stem cell transplantation (allo-HSCT).

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

The present study included 182 consecutive patients at IEO treated with PARPi for EOC between 2010 and 2021. Most patients (n = 103, 57%) received PARPi through open clinical trials, 24 (13%)

**TABLE 1** Main clinical features of 182 patients with epithelial ovarian cancer (EOC) with and without therapy-related myeloid neoplasms (t-MN) following poly(ADP-ribose) polymerase inhibitors (PARPi) and previous poly-chemotherapy

Characteristics	Patients without t-MN (n = 166)	Patients with t-MN (n = 16)
Median age at EOC diagnosis	54 (range 33-78)	52 (range 39-69)
Histology, n (%)		
Serous carcinoma	144 (87%)	15 (94%)
Endometrioid carcinoma	7 (4%)	1 (6%)
Clear cell carcinoma	5 (3%)	0
Mixed carcinoma	5 (3%)	0
NOS carcinoma	5 (3%)	0
Grade, n (%)		
High	156 (94%)	15 (94%)
Intermediate	4 (2%)	1 (6%)
Unknown	6 (4%)	0
FIGO stage, n (%)		
I	7 (4.5%)	0
II	7 (4.5%)	2 (13%)
III	119 (71%)	13 (81%)
IV	33 (20%)	1 (6%)
Germline BRCA1/2 status, n (%)		
Mutated	79 (47.5%)	9 (56%)
Wild type/VUS	68 (41%)	5 (31%)
Unknown <sup>a</sup>	19 (11.5%)	2 (13%)
Prior chemotherapy lines before PARPi, n (%)		
1-2	64 (38%)	8 (50%)
3-4	64 (38%)	5 (31%)
≥5	38 (24%)	3 (19%)
Type of PARPi, n (%)		
Olaparib <sup>b</sup>	100 (60%)	9 (56%)
Niraparib	63 (38%)	6 (38%)
Rucaparib <sup>b</sup>	4 (2%)	1 (6%)
PARPi therapy, n (%)		
Treatment	56 (34%)	1 (6%)
Maintenance	111 (66%)	15 (94%)
Duration of PARPi therapy, n (%)		
Median (months)	7.4 (range 0.8-110.8)	18.5 (range 4.1-42.2)
≤6 months	74 (45%)	3 (19%)
7-17 months	55 (33%)	3 (19%)
≥18 months	37 (22%)	10 (62%)
Presents status, n (%)		
Dead	54 (32%)	12 (75%)
Alive	94 (57%)	4 (25%)
Lost at follow-up	18 (11%)	0

Abbreviations: BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; VUS, variant of uncertain significance.

<sup>a</sup>Patients were enrolled in a 2010 clinical trial that did not require assessment of the BRCA status.

<sup>b</sup>A single patient received both olaparib and rucaparib as maintenance.

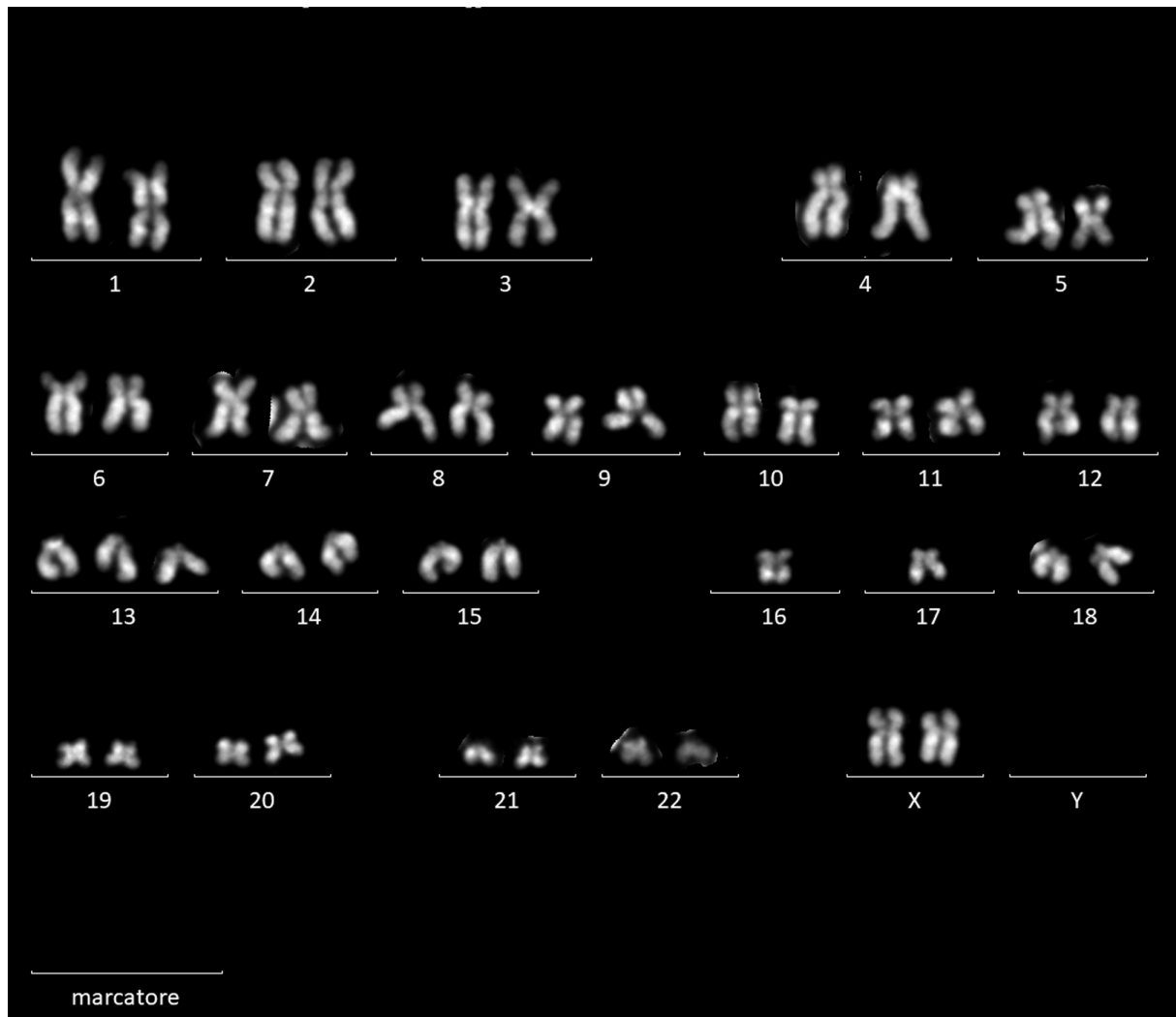
received PARPi as compassionate use and 55 (30%) after regular approval of the drug. One patient received olaparib within the SOLO2 trial and rucaparib as compassionate use. Among patients enrolled in

clinical trials, 63 (61.5%) received PARPi as monotherapy, whereas 40 (38.5%) received the cediranib-olaparib combination, as part of a randomized phase II study for patients with recurrent platinum-resistant

**TABLE 2** Main clinical and molecular features of 16 patients developing therapy-related myeloid neoplasms and their treatments

Type of t-MNs	EOC status at t-MN	Type and cycle of PARPi	Hematologic Toxicity	Duration (months)	Karyotype	Molecular biology <sup>a</sup>	Treatment administration	Type of CT administered	Allo-HSCT	CR duration (months)	Relapse	Salvage CT	Present status (dead/alive)	Cause of death
1 EB-2	NED	Olaparib (41 cycles)	N G2-3	2	46,XX, del(5)(q12q33), +13, -16, del(17)(p12pter) [cp12]/46,XX[6]	Mut. TP53 p.(Cys242Tyr) VAF 52%	Y	ICE → RD FLAG-Ida → CR	Y	5.4	Y	Decitabine + Venetoclax → RD → phase I trial	Dead	t-MN PD
2 AML	NED	Niraparib (10 cycles)	T G1 and N G2	1	79-98,XXXX, +3-4mar [cp11]	Mut. TP53 p.(His193Leu) VAF 91%	Y	Vyxeos	N	na	na	na	Dead	t-MN PD
3 EB-1	NED	Niraparib (25 cycles)	A G2, T G2 and N G3	1	46,XX, del(5)(q22q35) [3]/45,XX, del(5)(q22q35), -7, +8, +mar [2]/45,XX, del(5)(q22q35), -7[1]/45,XX, del(5)(q22q35), -7, +8, -17[1]/46,XX[3]	Mut. TP53 p.(Arg175His) VAF 20.05%	Y	Vyxeos	Y	4.7	Y	nd	Dead	t-MN PD
4 EB-1	CR	Olaparib (24 cycles)	A G2, T G2 and N G2	1	46,XX, del(5)(q22q35), -7, +8, -8, -17[10]/46,XX, del(5)(q22q35), -17 [3]/46,XX[2]	mut. TP53 p.(Arg249Thr) VAF 53.8%	Y	Vyxeos	N	2.8	N	na	Dead	Heart failure
5 AML M6	SD	Olaparib (29 cycles)	A G2 and T G3	1	46,XX[2]	Mut. TP53 p.(His179Arg) VAF 9.6%	Y	ICE → RD FLAG-Ida → RD decitabine+ven	N	na	NA	Decitabine + ven → RD	Dead	t-MN PD
6 EB-2	CR	Niraparib (19 cycles)	A G2, T G1, N G1	2	43,XX, t(1;12)(p21;p13), -7, -13, -16, -18, +mar [12]/46,XX[1]	Mut. TP53 p.(Val216Met) VAF 40.55%	Y	ICE ARA-C 6 g/mq	Y	4.7	Y	Ven → RD	Dead	t-MN PD
7 AML	SD	Rucaparib (26 cycles)	A G2, T G2, N G4	2	46,XX, del(13)(q12q14) [2]/46,XX[20]	Mut. TP53 p.(Arg273Cys) VAF 8%	Y	ICE ARA-C 6 g/mq	Y	49.3	N	na	Alive	na
8 EB-1	NED	Olaparib (21 cycles)	A G1 T G2	10	48-52,XX, +1, -5, -6, +8, +11, der(17)t(17;2)(p11.2;2), +19 +22, +2 mar[10]	Mut. TP53 p.(Pro151Arg) VAF 53.3%	Y	ICE	Y	15.6	N	na	Dead	TRM (PTLD)
9 EB-2	SD	Niraparib (21 cycles)	Pancytopenia and blasts	Immediate hematologic consult	46,XX,t(3;21)(q26;q22) [3]/46,XX[17]	mut. SH2B3 tras fus RUNX1(4)-MECOM[2]	Y	Vyxeos	Y	14.3	N	na	dead	TRM (GVHD)
10 EB-1	CR	Olaparib (33 cycles)	T G1 and A G2	10	44XX -7, del5, t(5;18)(q11.2); del5(q11)-18 [11]/46,XX	nd	Y	5-aza	Y	48.7	N	na	Alive	na
11 AML	SD	Olaparib (18 cycles)	A G2, T G2 and N G1	1	43-45,XX, -3, del(5)(q22q35), der(7) t(3;7)(2q21;2p21), -17, add (21)(q22), -22, +2mar [3]/46,XX[12]	Mut. TP53 p.(Met246Val) VAF 6.65% mut. TP53 p.(Ser241Tyr) VAF 33.4%	Y	5-aza + ven → RD	N	na	na	na	Dead	t-MN PD





**FIGURE 1** Karyotype (QFQ-banding) of patient ID #1 (Table 2). Karyotype equals 46, XX, del(5)(q12q33), +13, -16, -17; an example of deletion of chromosome 5 and loss of chromosome 17

ovarian cancer.<sup>13</sup> Four patients from double-blind clinical trials were included in the present analysis after unblinded procedures revealed that they had received the PARPi treatment. The main patient characteristics are reported in Table 1.

## 2.2 | PARP inhibitor treatments

Three different types of PARPi were employed and delivered orally: olaparib at 800 mg/day (capsule formulation) or 600 mg/day (tablet formulation); niraparib at 300 mg/day or rucaparib at 1200 mg/day. Most patients had been heavily pretreated, and 110 (60%) of them had received three or more lines of chemotherapy. In most cases, PARPi was administered as maintenance treatment after partial response or complete response (CR) was achieved after platinum-based chemotherapy; in the remaining 57 (31%) patients, PARPi was given as therapy for recurrent disease. PARPi was interrupted in case of disease progression or unacceptable toxicity. Patients receiving

PARPi for  $\geq 18$  months were identified as long responders (Table 1). Treatment toxicities were defined and graded according to the Common Terminology Criteria for Adverse Events.<sup>14</sup>

## 2.3 | Hematological and molecular investigations

Peripheral blood (PB) samples were collected prior to administration of a PARPi, then at monthly intervals and at the beginning of every new cycle. In addition to complete cell blood counts (CBCs), patients displaying persistent and/or marked hematological abnormalities underwent bone marrow (BM) evaluation including morphological, immunophenotypic, cytogenetic and fluorescent in situ hybridization (FISH) analysis. Identification of mutations or alterations in gene expression for routine clinical analysis was performed using the diagnostic Oncomine Myeloid Research Assay, a commercially available NGS assay investigating mutations and fusion transcripts in the 69 genes related with most frequency to myeloid malignancies

**TABLE 3** Allogeneic hematopoietic stem cell transplantation: Details of the procedure and outcomes

t-MNs	t-MN status at PBSCT	EOC status	MAC/RIC	Conditioning regimen	Source SC	HLA compatibility	GVHD prophylaxis	Number of CD34 <sup>+</sup> cells infused/kg	Graft failure	Acute GvHD	Chronic GvHD	MN best response	EOC best response	Relapse	Cause of death
1	EB-2 mCR	NED	MAC	Treo-Flu <sup>a</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup>	4.4 × 10 <sup>6</sup>	No	No	No	CR	NED	Yes	t-MN PD
2	AML cyCR	NED	MAC	Treo-Flu <sup>a</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup>	4.6 × 10 <sup>6</sup>	No	Yes (G2)	No	CR	NED	Yes	t-MN PD
3	EB-2 mCR	CR	MAC	Treo-Flu <sup>a</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup>	5.3 × 10 <sup>6</sup>	No	No	No	RELAPSE	SD	Yes	t-MN PD
4	AML cyCR	SD	MAC	Treo-Flu <sup>a</sup>	PBSC	Identical	MTX + CSA <sup>c</sup>	5.3 × 10 <sup>6</sup>	No	Yes (G2)	Yes	CR	CR	No	Alive
5	EB-1 mCR	NED	MAC	Treo-Flu <sup>a</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup>	5.6 × 10 <sup>6</sup>	No	No	No	CR	NED	No	TRM (PDTL)
6	EB-2 cyCR	SD <sup>2</sup>	MAC RIC	Treo-Flu <sup>a</sup> Flu-CTX-TBI <sup>d</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup> CTX post reinfusion + MMF + TAC <sup>b</sup>	4.8 × 10 <sup>6</sup> 6.4 × 10 <sup>6</sup>	Yes	Yes (G2) Yes (G4)	No	CR CR	SD SD	No	TRM (GVHD)
7	EB-1 cyCR	CR	MAC	Thio-Flu- Busulfan <sup>e</sup>	PBSC	Haploidentical	CTX post reinfusion + MMF + TAC <sup>b</sup>	3.9 × 10 <sup>6</sup>	No	No	Yes	CR	CR	No	Alive

Abbreviations: AML, acute myeloid leukemia; CR, complete response; cyCR, cytogenetic complete remission; EB1, myelodysplastic syndrome with excess blasts type 1; EB2, myelodysplastic syndrome with excess blasts type 2; EOC, epithelial ovarian cancer; GVHD, graft-vs-host disease; HLA, human leukocyte antigen; MAC, myeloablative conditioning; mCR, morphological complete remission; NED, no evidence of disease; PBSC, peripheral blood stem cell; PD, progression disease; PTDL, posttransplant lymphoproliferative disease; RIC, reduced intensity conditioning; SC, stem cells; SD, stable disease; t-MNs, therapy related myeloid neoplasms; TRM, transplant-related mortality.

<sup>a</sup>Treosulfan 14 g/smq day (-6; -5; -4) and Fludarabine 30 mg/smq day (-6; -5; -4; -3; -2).

<sup>b</sup>Cyclophosphamide (CTX) 50 mg/kg day (+3; +4) and mycophenolate mofetil (MMF) 15 mg/kg i.i.d. up to day +35 + Tacrolimus (TAC) from day +5 to day +100 (target Tacrolimus level 5-15 ng/mL) or Cyclosporine (CSA) from day -1 to day +100 (range 150-300 mg).

<sup>c</sup>Methotrexate 15 g/kg day +1, methotrexate 10 mg/kg day (+3; +6) and Cyclosporine from day -1 to day +100 (range 150-300 mg).

<sup>d</sup>Cyclophosphamide (CTX) 14.5 mg/kg day -6 → day -5, TBI 200 cGy.

<sup>e</sup>Thiotepa (Thio) 5 mg/kg day(-7; -6) and Fludarabine (Flu) 50 mg/smq day (-5; -4; -3) and Busulfan 3.2 mg/kg day(-5; -4; -3); Fludarabine 30 mg/smq day -6 → day -2.

**TABLE 4** Characteristics and management of five patients with pre-MDS hematological disorders

	Hematological abnormalities	PARPi (no cycles)	Karyotype analysis	Mutations (VAF) <sup>a</sup>	Diagnosis	Morphology (WHO criteria)	PARPi management
ID1	Erythroblastosis with H-Jolly bodies	Olaparib (14)	46,XX[8]/46,XX, inv(17)(q21q25)	TP53 (6.10%)	CCAUS	Normal	Stop
ID2	N G3 and T G2	Olaparib (26)	45,XX, del(5)(q22q35), -17[6]/46,XX[15]	TP53 (12%)	CCUS	Normal	Stop
ID3	A G3 and T G2	Niraparib (4)	nd <sup>b</sup>	Negative	ICUS (transient)	Normal	Continued
ID4	N G2	Olaparib (6)	nd <sup>b</sup>	Negative	ICUS (transient)	Normal	Continued
ID5	A G2	Olaparib (13)	nd <sup>b</sup>	Negative	ICUS (transient)	Normal	Continued

Abbreviations: A, anemia; CCAUS, clonal cytogenetic abnormalities of undetermined significance; CCUS, clonal cytopenia of undetermined significance; G, grade according to Common Terminology Criteria for Adverse Events; ICUS, idiopathic cytopenia of undetermined significance; N, neutropenia; PARPi, poly(ADP-ribose) polymerase inhibitors; T, thrombocytopenia; transient, recovery after PARPi interruption and recurring after PARPi resumption; VAF, variant allele frequency.

<sup>a</sup>Next generation sequencing analysis of PB DNA using OncoPrint Myeloid Research Assay and the Ion Torrent S5 technology (ThermoFisher).

<sup>b</sup>Nd, not done, due to only transient blood counts abnormalities and no detectable mutations by NGS.

(Table S1). Analysis was performed with IonReporter software applying the last release of Myeloid workflow (ThermoFisher).

To identify mutations for research purposes, we used a custom gene panel, the Myelo-panel. The purpose of this analysis was to identify germline variants from buccal DNA and somatic variants from PB that are associated with a predisposition to developing myeloid neoplasms, and to stratify patients for possible targeted therapies. DNA was extracted from buccal swabs and from PB using the QIAamp DNA mini kit (Qiagen) following the manufacturer's instructions. Our custom Myelo-panel analyzes 255 cancer-predisposing genes (Table S2), including: susceptibility genes, which are those most frequently associated with the risk of development of hematological tumors; AML drivers, which play a key role in leukemogenesis; actionable genes, defined as genes that have a concrete clinical manageability for which either a US Food and Drug Administration-approved or clinical trial drug is available; and pharmacogenomics single nucleotide polymorphisms (SNPs), allelic variants associated with susceptibility to certain drugs. The sources for our 164 actionable genes and 127 pharmacogenomics SNPs were the Alleanza Contro il Cancro (ACC) Database, based on DGIb (15); the dGene (annotation tool for cancer genome sequencing data<sup>16</sup>; PharmGKB (The Pharmacogenomics Knowledgebase, [www.pharmgkb.org/](http://www.pharmgkb.org/)); and literature mining.<sup>17</sup> Targeted capture was carried out according to manufacturer's protocols using the AmpliSeq kit and Ion Torrent sequencing. Variant analysis was performed with IonReporter software (ThermoFisher Scientific). Identified variants were annotated in terms of pathogenicity, using different computational tools, including ClinVar, Varsome and RENOVO (see Supporting Information Materials and Methods in Appendix S1 for details). The sequencing coverage and quality statistics for each sample are summarized in Tables S3 and S4.

The World Health Organization (WHO) 2016 Classification was used to define myelodysplastic syndrome (MDS) and acute leukemias (AL) subtypes.<sup>18</sup> The Revised International Prognostic Scoring System (IPSS-R)<sup>19</sup> was employed to define the MDS prognostic score, and the European Leukemia Network (ELN) was used for AML.<sup>20</sup> Pre-MDS conditions included idiopathic cytopenia of undetermined significance

(ICUS), idiopathic dysplasia of unknown significance (IDUS), clonal hematopoiesis of indeterminate (clinical) potential (CHIP), clonal cytopenia of unknown significance (CCUS) and clonal cytogenetic abnormalities of undetermined significance (CCAUS). These conditions can be divided into: (a) cytopenic states (ICUS and CCUS) or noncytopenic states (IDUS, CHIP, CCAUS) and (b) states with an unknown or negative mutation status (ICUS and IDUS) or cases with known (documented and relevant) somatic mutations/cytogenetic abnormalities (CHIP, CCUS and CCAUS). All of these conditions can persist without clinical manifestation or progression, but can develop into overt MDS.<sup>21,22</sup> Hematological procedures were performed according to internal institutional diagnostic and clinical guidelines.

## 2.4 | Statistical methods

Only descriptive statistics were used to report data related to patient demographics, clinico-pathological characteristics and treatments in Table 1.

## 3 | RESULTS

### 3.1 | Therapy-related myeloid neoplasms: Diagnosis and clinical presentation

Overall, 16 of 182 (8.7%) patients with EOC treated with PARPi as salvage after chemotherapy developed t-MNs. As shown in Table 2, the occurrence of t-MDS was preceded by one or more hematopoietic-line cytopenia of varying duration, from a few days to 10 months after PARPi discontinuation. In particular, five patients developed a t-MDS with multilineage dysplasia (MLD), and seven had a MDS with excess of blasts (EB) (four EB1 with BM blasts 5%-9%, three EB2 with BM blasts 10%-19%). The four cases of t-AML evolved from cytopenias within 60 days after PARPi withdrawal.



**TABLE 5** Germline and somatic mutations identified in patients with persistent cytopenia and clonal hematopoiesis by analysis with the custom Myelo panel

ID	Germline mutations <sup>a</sup>				Somatic mutations <sup>a</sup>				Gene classification <sup>c</sup>		
	Gene	Type	VAF (%)	AA substitution	Variant annotation <sup>b</sup>	Gene	Type	VAF (%)		AA substitution	Variant annotation <sup>b</sup>
1	BRCA1	INDEL	51.4	p.Leu1679TyrfsTer2	Pathogenic	IGFN1	SNV	17.9	p.Gly1565Asp	VUS	AML Driver
						NBEAL2	SNV	3.1	p.Leu1093Val	VUS	AML driver
						TP53	SNV	7.2	p.Cys238Tyr	Pathogenic	AML driver/susceptibility
2	BRCA1	INDEL	51.6	p.Asn363IlefsTer11	Pathogenic	EPHA4	SNV	2.5	p.Cys191Arg	VUS	Actionable
						TP53	SNV	4.8	p.Cys176Ser	Pathogenic	AML driver/susceptibility
3	NONE					GNA11	SNV	3.2	p.Leu40Phe	Likely pathogenic	Actionable
4	BCR	INDEL	56.8	p.Lys754AsnfsTer34	Pathogenic	EPHB2	SNV	52.9	p.Gln626Arg	Likely pathogenic	Actionable
						NOTCH1	SNV	40.5	p.Thr2090Met	VUS	Actionable
						SLTM	SNV	52.2	p.Gln54Arg	Likely pathogenic	Actionable
						BRCA1	SNV	45.3	p.Arg1495Met	Pathogenic	Susceptibility/actionable
5	NONE					NOTCH1	SNV	3.2	p.Asn104Thr	VUS	Actionable

Abbreviations: AA, aminoacidic; AML, acute myeloid leukemia; INDEL, insertion/deletion; SNV, single nucleotide variant; VAF, variant allele frequency; VUS, variant of uncertain significance.

<sup>a</sup>Next generation sequencing analysis using custom Myelo panel and the Ion Torrent S5 technology (ThermoFisher).

<sup>b</sup>Annotation of variants for pathogenicity by ClinVar, VarSome, RENOVO.

<sup>c</sup>Gene classification based on our gene lists in the customized Myelo panel; for definitions, see Section 2.3.

All 16 patients developing t-MNs were characterized cytogenetically and 13 of them were sequenced with the OncoPrint Myeloid Research Assay. Table 2 details our cytogenetic and molecular findings. Seven patients had del(5q)–5 and/or del(7q)–7, nine had a complex karyotype. An example of complex karyotype with both del(5q) and loss of chromosome 17 is given in Figure 1. A TP53 mutated gene was found in 12 out of 13 patients tested with the OncoPrint Myeloid Research Assay.

### 3.2 | Therapy-related myeloid neoplasms: Management

PARPi was discontinued in all patients developing t-MNs. Four patients were unable to receive any specific treatment for their t-MNs because of a rapid and fatal outcome. In detail, one patient had a sudden cardiac death while at home, one patient died from a massive brain hemorrhage and the two remaining patients died from rapid EOC progression. A fifth patient, with t-MDS-MLD and low IPSS-R score, is currently being monitored through a watch-and-wait approach, with excellent control of both the EOC and the hematological malignancy thus far.

Eleven patients underwent induction therapy, seven of whom then underwent allogeneic hematopoietic cell transplantation (allo-HSCT) (Tables 2 and 3). Treatment included intensive induction chemotherapy according to the ICE (idarubicin-etoposide-cytarabine) scheme in five patients or with Vyxeos liposomal therapy in four patients (Table 2). The remaining two patients received low-intensity treatment, one with 5-azacitidine alone and the other with 5-azacitidine plus venetoclax.

Three of eleven patients (27%) had primary refractory disease and died from leukemia progression, whereas eight patients experienced CR, including five (46%) who achieved cytogenetic CR (cyCR) after Vyxeos liposomal therapy (three patients), ICE (one patient) or 5-azacitidine (one patient). The remaining three patients (27%) experienced morphological CR (mCR) with persistence of cytogenetic alterations.

One patient died from heart failure before allo-HSCT and while in cyCR, and the remaining seven patients underwent allo-HSCT from haplo-identical family donors (six patients) or from an HLA identical donor. At the time of allo-HSCT, four patients were in cyCR, three in mCR.

At present, two patients in cyCR are alive in persistent remission at 3 and 4 years, respectively, since allo-HSCT. Both of them experienced chronic graft-vs-host disease (cGVHD): one patient had a limited lung cGVHD that resolved after steroids, but the other patient had extensive skin cGVHD, requiring a variety of immunosuppressive treatments for more than 3 years. This patient recently experienced disease progression of her solid tumor, with an initial response after retreatment with platinum-based chemotherapy.

Five patients died after allo-HSCT. One patient in cyCR had relapse at 150 days after allo-HSCT, and the second patient in cyCR experienced a graft failure, was retransplanted and died of extensive

acute GVHD 30 days after the second procedure. Of the three patients in mCR, two died because of leukemia relapse (300 and 179 days after allo-HSCT, respectively) and one of a posttransplant lymphoproliferative disorder (PTDL) at +90 days.

At a median observation of 6.8 months (range 2.3-49), 3 of 16 patients (19%) were alive and 13 had died, 10 because of leukemia, 2 from transplant-related events and 1 from heart failure.

### 3.3 | Persistent cytopenia and clonal hematopoiesis

Five additional patients were referred to hematological consultancy for persistent CBC abnormalities after PARPi discontinuation. PB NGS (using the Oncomine Myeloid Research Assay) disclosed *TP53* mutations, in the absence of immunophenotypic abnormalities in two patients, whereas no myeloid neoplasm-related mutations were detectable in the remaining three patients. Patients harboring a *TP53* mutation (Table 4, IDs 1 and 2) underwent further hematological investigations that led to a diagnosis of CCAUS in one patient and CCUS in the second patient. The three patients with a negative NGS assay were classified as having ICUS (Table 4, IDs 3-5), with inadequate tolerance to PARPi, because of prolonged cytopenias after a short PARPi retreatment.

All five patients were also investigated using our customized Myelo-panel, which targets 255 cancer predisposing genes, as described in the Section 2. We analyzed buccal DNA for identification of germlines variants and PB for identification of somatic variants. As detailed in Table 5, we identified several variants of uncertain significance (VUS) in all patients. Patient ID1 (CCAUS) carried a *BRCA1* germline pathogenic mutation and two somatic variants (in AML driver genes *IGFN1* and *NBEAL2*<sup>23</sup>), in addition to the known *TP53* mutation. In patient ID2 (CCUS), we identified a *BRCA1* germline mutation and a somatic variant in *EPH4*, in addition to the known *TP53* mutation. In patients ID3 and ID5 (both ICUS), somatic mutations in *GNA11* and *NOTCH1* genes, respectively, were detected in the absence of germline abnormalities. In Patient ID4 (ICUS), we identified a pathogenic germline variant in *BCR* and four somatic mutations in *EPHB2*, *NOTCH1*, *SLTM* and *BRCA1*, all with an elevated variant allele frequency. Finally, in four patients, we identified mutations in “actionable” genes, although at low frequency (Table 5).

## 4 | DISCUSSION

The present report describes the occurrence of t-MNs in a series of 182 women receiving salvage PARPi for progressing EOC after chemotherapy treatments at our Milan Center during the last 11 years. Overall, 16 patients (8.7%) developed t-MNs after a median exposure time to PARPi of about 2 years. At a median observation time of 6.8 months (range 2.3-49), 3 of 16 (19%) patients were alive, two after allo-HSCT and one under watch-and-wait management for a low-risk t-MDS. Ten patients died because of leukemia-related adverse events,

two more from transplant-related events and one from heart failure. The study confirms that the risk of secondary myeloid neoplasms after chemotherapy and then PARPi cannot be minimized and indicates the poor prognosis for women developing t-MNs after salvage PARPi, despite early diagnosis and the use of effective therapies supplemented with allo-HSCT. The genetic complexity observed in patients developing hematological disorders related to therapy can explain to a certain extent these very poor outcomes.

A previous report by our group raised warnings about the risk of hematological disorders after salvage PARPi treatment.<sup>9</sup> In that study, we documented a markedly higher incidence of t-MNs compared to observations from large multicenter trials with PARPi thus far reported. We have extended our original study by close monitoring of all women referred to our center for salvage PARPi treatment for refractory/relapsed EOC. The extended analysis confirms the significant occurrence of t-MNs and the overall incidence of 8.7% is comparable to the 6.9% originally reported in our previous study. These numbers are in line with the results of two recent large studies with reported t-MNs incidences of 4.79% and 8%, respectively.<sup>8,12</sup> Thus, the occurrence of t-MNs is a serious and relevant complication in women with EOC exposed to PARPi after previous chemotherapy treatments.

Three patients in our study had a rapid and fatal outcome, and one patient continues with stable disease. The remaining 12 patients received adequate cytoreductive treatments, according to the most effective approaches, including the ICE schedule or the recently developed combined drug Vyxeos or demethylating agents with or without Venetoclax.<sup>24,25</sup> Most patients who experienced a response also underwent allo-HSCT, taking advantage of expanded donor availability using either identical or haploidentical donor sources.<sup>26</sup> Despite these prompt and quite effective treatments, 3 of 16 patients survived to the last follow-up, with one patient still free of solid and hematological tumors. This low survival indicates the particularly adverse prognosis of t-MNs occurring after salvage PARPi and the need to seek for treatment strategies specifically designed for these peculiar hematological neoplasms.

In this regard, it must be also underlined that PARP inhibitors currently used in the clinic target both PARP-1 and PARP-2 indiscriminately; however, despite some functional redundancy, it has been recently suggested that the tumorigenic role of the two proteins is related to the type of cancer. Indeed, in prostate cancers only PARP-2 is selectively upregulated and associated to prostate cancer growth and aggressiveness.<sup>27</sup> In a model of cMyc-driven lymphomagenesis, loss of PARP-2 protects from development of c-Myc-dependent lymphomas while loss of PARP-1 accelerates lymphomagenesis. However, no differences were observed on other models of leukemia such as Noct1-dependent T-ALL, where either loss of PARP-1 or PARP-2 had no effect on mouse survival.<sup>28</sup> These data underline the critical issue of developing selective PARPi to increase effectiveness and reduce possible side effects. In this perspective, AstraZeneca has developed a PARP-1-specific inhibitor, currently in Phase I clinical trial, that in *BRCA*-mutated breast cancer models, has shown higher anti-tumor efficacy compared to Olaparib (AstraZeneca's Petra Study, available at ClinicalTrials.gov-Identifier: NCT04644068).

Our t-MN patients were extensively investigated for genetic lesions, and various chromosomal alterations were found, including chromosome 5q deletion, partial or complete loss of chromosome 7 or a complex karyotype. These cytogenetic features are typical of t-MNs secondary to alkylating agents.<sup>29</sup> In addition, molecular testing identified *TP53* mutations in 12 of 13 tested patients. These *TP53* mutations frequently co-occurred with partial deletion, complete loss or rearrangement of chromosome 17 (Table 2), suggesting loss of heterozygosity (LOH) at the *TP53* locus in several patients of our cohort developing t-MNs. Recently, preexisting *TP53*-mutated clonal hematopoiesis was reported to be a risk factor for t-MNs in high-grade EOC patients treated with rucaparib, and an expansion of the *TP53* clone has been observed in patients developing MDS/AML. Furthermore, the presence of HR repair gene mutations in the tumor, either germline or somatic, including *BRCA1* and *BRCA2*, has been associated with increased incidence of MDS/AML.<sup>30</sup> It seems quite likely that the high frequency of *TP53* mutations and the numerous additional genetic lesions are responsible for the poor response to treatments, including allo-HSCT, observed in our patients with t-MNs after PARPi salvage therapy.<sup>31</sup>

It is not possible to establish which factor contributes most to the development of t-MNs, among the PARPi, prior exposure to chemotherapy (mainly alkylating agents) and the combination of these multiple cytotoxic treatments.<sup>32</sup> It is noteworthy that in our series, patients placed on PARPi maintenance after multiple prior lines of chemotherapy had the highest risk of t-MNs, suggesting that cumulative prior chemotherapy exposure may be a relevant factor for developing MDS/AML with prolonged salvage PARPi.<sup>8</sup> PARPi therapy has been recently approved for early use after first-line chemotherapy in newly diagnosed metastatic EOC. This should allow for a better understanding of the role of PARPi in leukemogenesis.<sup>33</sup> Both PARP1 and TP53 can bind the ends of broken DNA, acting as potential sensors and signaling molecules for the detection of double-strand breaks. PARP1-dependent poly-ADP ribosylation is increased in response to DNA damage, and TP53 mutants bind with enhanced efficiency to broken DNA ends. As a consequence, PARP1 inhibition in the presence of mutated TP53 may enhance genetic instability and drive leukemogenesis.<sup>34</sup> Exposure to cytotoxic drugs along with the inhibition of PARP activity and the possible presence of *TP53*-mutated clones may interact and contribute to the development of t-MNs.

The presence of genetic lesions predisposing and/or predicting t-MNs was supported by the deep analysis of five patients developing pre-MDS features. With our customized Myelo-panel, we found “actionable” mutated genes in all but one patient. Moreover, the finding of clonal hematopoiesis in the three “transient” ICUS patients allowed us to re-classify them within the CCUS subgroup. Patients harboring multiple somatic variants, with high allelic burden, need close follow-up because of the high risk of evolution into an overt t-MN. In such cases, pre-emptive treatment with target drugs might be an appealing option, and additional studies should focus on this issue. Careful diagnostic procedures are strongly recommended whenever “transient” cytopenias are observed during PARPi treatment. As recently advised, even minor hematological abnormalities might be an early safety signal, suggesting the need for attention and possible

PARPi discontinuation if required.<sup>35</sup> Furthermore, in the near future, PARPi will be used for broader indications in tumors for which a synthetic lethality approach is expected to be effective. In fact, olaparib has been recently approved for the treatment of *BRCA1/2*-mutated, HER2-negative breast cancer after courses of anthracyclines and taxanes.<sup>36,37</sup> Consequently, establishing a preventive measure for identification of gene mutations that may raise risk for t-MNs in patients treated with PARP inhibitors alone or as a salvage therapy after chemotherapy treatment is urgent and mandatory. In this view, a prospective biological study is ongoing among the gynecological, hematological and molecular research units at our center, aimed at identifying possible genetic abnormalities, associated with an increased risk for t-MNs after PARPi treatment, including mutations analysis in genes involved in CHIP.

In summary, our study confirms the actual risk of t-MN in EOC patients treated with chemotherapy and subsequently exposed to prolonged PARPi therapy. The management of these patients is quite complex and the outcome is extremely poor. In this context, a preventive approach based on the identification of gene mutations that may raise risk for t-MNs and “actionable” gene mutations is warranted and could be crucial for protecting these women from a second devastating and often incurable neoplasm.

#### AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. Conceptualization: Elisabetta Todisco and Corrado Tarella; Resources: Federica Gigli, Chiara Ronchini, Viviana Amato, Simona Sammassimo, Rocco Pastano, Gabriella Parma, Maria Teresa Lapresa, Francesco Bertolini, Chiara Corsini, Giuliana Gregato, Claudia Poletti; Formal analysis: Elisabetta Todisco, Chiara Ronchini, Giuliana Gregato; Supervision: Elisabetta Todisco, Nicoletta Colombo, Pier Giuseppe Pelicci, Myriam Alcalay, Francesco Bertolini and Corrado Tarella; Writing - original draft: Elisabetta Todisco, Federica Gigli, Chiara Ronchini and Corrado Tarella; Writing - review & editing: Elisabetta Todisco, Federica Gigli, Chiara Ronchini, Myriam Alcalay and Corrado Tarella.

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#### CONFLICT OF INTEREST

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon 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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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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