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Is BRCA mutational status a predictor of platinum-based chemotherapy related hematologic toxicity in high-grade serous ovarian cancer patients?

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HIGHLIGHTS

- BRCA1 and BRCA2 genes encode proteins essential for the repair of double-strand DNA breaks, through homologous recombination.
- Germline mutations of the genes BRCA1 and BRCA2 increased cancer predisposition.
- High-grade epithelial ovarian cancer is very sensitive to chemotherapy platinum-based.
- BRCA germline mutations is associated with greater hematological toxicity in ovarian cancer patients.

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ABSTRACT

Objective. To evaluate hematologic adverse effect profiles associated with frontline platinum-based chemotherapy in ovarian cancer patients according to BRCA 1/2 mutational status.

Methods. Patients with high-grade serous ovarian cancer and a known BRCA mutational status who received in frontline 6 cycles of Carboplatin (AUC 5) plus Paclitaxel 175 mg/mq were retrospectively selected from our databases. Hematologic toxicity profiles of BRCA mutated patients were compared to non-mutated patients, according to EORTC Common Terminology Criteria for Adverse Events (CTCAE_4.02).

Results. Totally, 176 women of whom 58 (33%) were BRCA1/2 mutation carriers - 40 BRCA1 (69%) and 18 (31%) BRCA2 mutations carriers - and 118 (67%) non-carriers were identified.
A significant higher frequency of thrombocytopenia (24% vs 5%; $p < 0.001$), anemia (21% vs 7%; $p = 0.006$) and neutropenia (62% vs 27%; $p \leq 0.001$) was observed in BRCA mutated patients, resulting in a higher percentage of granulocyte-colony stimulating growth factors injection (12% versus 1%, $p < 0.001$) and dose delay (19% versus 27%, $p = 0.005$). The multivariate analysis confirmed that granulocyte-colony stimulating growth factors injection and dose delay were statistically significantly more frequent in BRCA mutated patients (OR 2.567, 95% CI 1.136–5.798, $p = 0.035$; OR 3.860, 95% CI 1.098–13.570, $p = 0.023$). Finally, the total number of hematologic adverse events compared between the two groups of patients during the entire treatment period showed a substantial higher rate of hematologic adverse events in BRCA mutated population.

Conclusions. Germline BRCA 1/2 mutations are associated with a higher hematologic toxicity in patients with ovarian cancer who underwent platinum-based chemotherapy.

1. Introduction

Ovarian cancer (OC) represents the most lethal gynecological cancer in developed countries, accounting 99,800 new cases and 65,900 deaths related to the disease [1].

Primary de-bulking surgery followed by adjuvant platinum-based chemotherapy is the standard treatment for advanced disease with minimal or absent residual disease after cytoreductive surgery being the most important prognostic factor.

Although growing surgical and medical attempts are improving the efficacy of treatments, the majority of OC patients developed recurrent disease.

BRCA1 and BRCA2 genes have been showed to be integrally involved in the repair of DNA double-strand breaks by homologous recombination, thus predisposing to different tumors onset. Indeed, the female

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BRCA mutation carrier's lifetime risk of developing OC is approximately 16–44% with a BRCA 1 mutation and to 16–27% with a BRCA 2 mutation [2–4]. In the last decades since these cancer susceptibilities genes were first identified, an increasing understanding of the molecular and cellular roles of the proteins they encode has emerged and their roles in maintaining genomic integrity and regulating cellular proliferation have been described [5–10]. Moreover, somatic loss of wild-type BRCA allele (loss of heterozygosity [LOH]) is believed to be an important early step for BRCA-related tumorigenesis, and there is increasing interest in whether the inheritance of 1 mutant allele, and possible resultant haploinsufficiency in 1 or another organ system, is sufficient for cancer predisposition or, indeed, other phenotypic effects [11].

Given that cells of women with a germline BRCA mutation have 1 mutant and 1 functional allele, it has been suggested that potentially lower cellular levels of BRCA protein may lead to a reduced ability to repair chemotherapy induced DNA damage, resulting in greater treatment-related toxicities. In particular, it is plausible that an actively dividing population of non cancer cells in BRCA heterozygotes, such as hematopoietic stem cells, would sustain greater DNA damage in response to platinum-based chemotherapy (the mainstay of OC treatment), resulting in increased myelosuppression as manifested by anemia, neutropenia, and/or thrombocytopenia [10].

Thus, the aim of this study was to evaluate the hematologic toxicity profile associated to frontline chemotherapy in patients affected by high-grade serous ovarian cancer according to BRCA1-2 mutational status.

2. Materials and methods

2.1. Patients selection

For this retrospective cohort study, we selected from our electronic database a cohort of women who referred at the Department of Maternal and Child Health and Urological Sciences University of Rome (Sapienza) from January 2004 to September 2017 for a primary diagnosis of high grade serous OC with a known BRCA1-2 mutational status.

All patients included in our study received 6 cycles of platinum-based (three-weekly Carboplatin AUC5 and Paclitaxel 175 mg/mq) adjuvant chemotherapy or 3 cycles of neoadjuvant chemotherapy followed by interval de-bulking surgery and other 3 cycles of chemotherapy whit the same regimen. All patients who had been treated for ovarian cancer with surgery and platinum- based chemotherapy before the introduction of the screening for BRCA 1/2 mutational status were tested years over the diagnosis.

Recent cases were tested at the diagnosis. All patients included in our study were affected by primary high grade serous ovarian cancer with a known BRCA mutational status and underwent to primary de-bulking surgery followed by adjuvant platinum-based chemotherapy. All our patients were tested with the same Next Generation DNA Sequencing essay (including those at their primary diagnosis and those with relapsed disease who were potentially amenable of Parp inhibitor treatment.).

Thus, patients were selected through the following inclusion criteria:

- known BRCA1-2 mutational status,
- histologically confirmed high grade serous OC,
- first-line platinum-based chemotherapy,
- age above 18 years,
- performance status Eastern Cooperative Oncology Group (ECOG) 0,
- peripheral blood count, and renal and liver function within normal values at baseline,
- the availability of a complete medical documentation, including all toxicity data reported cycle by cycle.

Patients with BRCA mutations classified as variants of uncertain significance (VUS) were excluded from final analysis.

All women gave a written informed consent for their data to be collected and analyzed for scientific purposes. The Institutional Review Board approved the study.

Patients were subdivided into two groups: BRCA 1 or 2 mutated patients and non-mutated ones.

For each cycle of chemotherapy we reviewed the hematological toxicity outcomes by evaluating the absolute value of hemoglobin, platelets and neutrophils, the necessity for growth factors and any delay in the administration of the subsequent cycle or reducing the dose of chemotherapy.

Of note, the use of growth factors in our department usually follows national and international guidelines in a strict manner.

2.2. Statistical analysis

Statistical analysis was carried out using SPSS Statistic 25 software. Differences in mean distribution was calculated through a Students' T-Test. Chi Square test was used for data comparison of categorical variables. All results statistically significant were included at multivariate analysis in order to confirm their significance. The impact of BRCA mutational status on the total number of hematologic adverse events during the entire treatment period was evaluated through the ratio of the sum of single episodes on the total number of cycles of chemotherapy and comparing these frequencies using Chi Square test according to BRCA mutational status.

p-Values < 0.05 were considered statistically significant.

3. Results

We totally analyzed 176 women of which 58 BRCA1/2 mutation carriers - 40 BRCA1 and 18 BRCA2 mutations carriers - and 118 non-carriers.

Table 1 reports clinical characteristics of patients, comparing them between the two groups.

As observable, there was a statistically significant difference in age between mutated and non-mutated BRCA patients (57.93 ± 11.87 vs 52.34 ± 7.22; $p < 0.01$). Moreover, as regards the characteristics of the tumor, there was a higher frequency of stage III and IV FIGO in BRCA patients mutated compared to non-mutated patients, and this difference was statistically significant (96.6% vs 84.7%; P 0.02).

Table 2 represents the general toxicity profile according to BRCA mutational status.

These data suggest that BRCA mutated patients were more frequently associated to at least 1 episode of hematologic toxicity in terms of number of platelets $<150 \times 109$/L (24% vs 5%; $p < 0.001$), in the frequency of hemoglobin <10 g/dL (21% vs 7%; $p = 0.006$), in absolute neutrophil count $<1.5 \times 109$/L (62% vs 27%; $p \leq 0.001$), resulting in a statistically significantly higher percentage of granulocyte-colony stimulating growth factors injection (35% versus 5%, $p < 0.001$) and dose delay (48% versus 27%, $p = 0.005$).

Including in a multivariate analysis all covariates that were significant at univariate analysis, granulocyte-colony stimulating growth

Table 1
Patients' clinical characteristics.

Characteristic	Overall population (n = 176)	BRCA1/2 mutated (n = 58)	BRCA1/2 wild-type (n = 118)	p-Value
	(Mean ± SD)			
Age	56.09 ± 10.87	52.34 ± 7.22	57.93 ± 11.87	**<0.001**
	Number (%)			
Stage FIGO				
I–II	20 (11.4%)	2 (3.4%)	18 (15.3%)	**0.02**
III–IV	156 (86.6%)	56 (96.6%)	100 (84.7%)	

p-Value was estimated using a Chi-square Pearson's test or Students' T-Test.
SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics; NI, not indicated; n, number.

Table 2
Hematological toxicity profiles according to BRCA mutational status.

Toxicity	BRCA1/2 mutated (n = 58)	BRCA1/2 wild-type (n = 118)	*p*-Value
Platelets <150 × 10^9/L	14 (24%)	6 (5%)	<**0.001**
Hemoglobin <10 g/dL	12 (21%)	8 (7%)	**0.006**
Absolute neutrophil count <1.5 × 10^9/L	36 (62%)	32 (27%)	<**0.001**
G-CSFs injection	20 (35%)	6 (5%)	<**0.001**
Dose reduction	18 (31%)	32 (27%)	0.588
Dose delay	28 (48%)	32 (27%)	**0.005**

p-Value was estimated using a Chi-square Pearson's test.
G-CSFs, granulocyte-colony stimulating growth factors; n, number.

factors injection and dose delay were statistically significantly more frequent in BRCA mutated patients (OR 2.567, 95% CI 1.136–5.798, $p = 0.035$; OR 3.860, 95% CI 1.098–13.570, $p = 0.023$).

We analyzed frequencies of hematologic toxicity, extrapolated by hemoglobin, platelets and neutrophils values through each cycle of platinum-based chemotherapy, according to BRCA mutational status.

The percentage of patients who experienced at least one episode of anemia was similar between the two groups for the first 2 cycles of chemotherapy. However, we observed a statistically significant higher percentage of patients with anemia in BRCA mutation carriers compared to non-carrier patients after the third, the fourth, the fifth and the sixth cycle of chemotherapy but in none of these patients the toxicity did not rise a third grade of anemia according to the EORTC CTCAE scale.

In detail, the percentage of anemia in BRCA mutation carriers compared to non-carrier patients was of grade I–II in 10.3% versus 1.7% with no grade III–IV in both groups ($p = 0.01$) after the third cycle, of grade I–II in 10.3% versus 1.7% with no grade III–IV in both groups ($p = 0.01$) after the fourth cycle of chemotherapy, of grade I–II in 13.8% versus 1.7% with no grade III–IV in both groups ($p = 0.001$) after the fifth cycle, of grade I–II in 20.7% versus 3.4% with no grade III–IV in both groups ($p \leq 0.01$) after the sixth cycle of chemotherapy.

In the same way, the percentage of patients with neutropenia appeared significantly greater in the BRCA mutation carriers from the second cycle.

The frequency of patients with neutropenia in BRCA mutation carriers compared to non-carrier patients was of grade I–II in 6.9% versus 11.9% with grade III–IV in 13.8% versus 3.4% ($p = 0.02$) after the second cycle, of grade I–II in 13.8% versus 3.4% with grade III–IV in 17.2% versus 0 ($p \leq 0.01$) after the third cycle, of grade I–II in 13.8% versus 3.4% with grade III–IV in 17.2% versus 0; ($p \leq 0.01$) after the fourth cycle, of grade I–II in 17.2% versus 6.8% with grade III–IV in 10.3% versus 3.4% ($p = 0.01$) after the fifth cycle and of grade I–II in 31% versus 3.4% with grade III–IV in 13.8% versus 0 ($p < 0.001$) after the sixth cycle of chemotherapy.

As regards the frequency of thrombocytopenia appeared to be greater in BRCA mutated patients than in the non-mutated, but this difference was not statistically significant.

Fig. 1 represents the graphical distribution of the rates of anemia and neutropenia per cycle among OC patients underwent chemotherapy, according to BRCA mutational status.

Table 3 shows the total number of hematologic adverse events compared between the two groups of patients during the entire treatment period consisting of 348 and 708 cycles of chemotherapy administered at BRCA mutated and BRCA wild type patients respectively.

A statistically significant difference has been shown both in the number of platelets <150 × 109/L (5.75% vs 1.41%; $p \leq 0.01$), in the frequency of hemoglobin <100 g/L (10.34% vs 1.98%; $p \leq 0.01$), in absolute neutrophil count <1.5 × 109/L (26.44% vs 7.06%; $p \leq 0.01$).

Likewise, a significantly higher frequency of granulocyte-colony stimulating growth factors use was reported in BRCA mutated patients compared to non-mutated (12.07% vs 1.41%; $p < 0.001$).

Moreover, we observed a greater frequency of dose reduction (8.62% vs 5.37%; $p = 0.22$) and dose delay (18.96% vs 9.89%; $p = 0.08$) in BRCA mutated compared to non-mutated patients but this difference was not statistically significant.

Finally, we tried to evaluate if in patients who underwent neoadjuvant chemotherapy followed by interval de-bulking surgery the toxicity might be higher.

As observable in Table 3, all patients with BRCA mutation had higher toxicity from the second cycle of chemotherapy. Thus, it is easily deducible that hematologic toxicity profile was similar in patients treated by a neoadjuvant approach. Indeed, analyzing hematologic toxicity per cycle, the trend is similar to that of whole population (Fig. 2).

4. Discussion

Our data suggest that BRCA mutational status is more frequently associated to hematologic toxicity in terms of anemia, neutropenia and thrombocytopenia, resulting in a statistically significantly higher percentage of granulocyte-colony stimulating growth factors injection and dose delay.

Moreover, we observed a greater frequency of anemia and neutropenia from the third and second cycle of chemotherapy respectively with a rising statistically significant trend.

It therefore appears that, as the number of chemotherapy administrations increases, the difference in chemo-related toxicity between the two groups also increases.

The total number of hematologic adverse events compared between the two groups of patients during the entire treatment period showed a substantial higher rate of hematologic adverse events, not leading to dose delay (even of a trend has been observed) or dose reduction.

However, granulocyte-colony stimulating growth factors injection was statistically significantly more frequently administered in mutation carriers.

These results seem to confirm the hypothesis sustaining the increased myelosuppressive potential associated to chemotherapy in BRCA mutated patients.

After its first discovery, deficiency in homologous recombination due to deleterious BRCA1/2 gene mutations has been progressively recognized not only as a predictor of ovarian cancer susceptibility, but also as a prognostic factor.

Platinum-based chemotherapy induces the production of DNA double-strand breaks in their repertoire. As the BRCA genes are involved in the homologous repair of DNA double-strand breaks, not only the tumor but also the normal tissues in BRCA heterozygotes could have increased sensitivity to chemotherapeutic agents. [12,13]

However, only a few studies have been conducted on hematological toxicity related to BRCA mutation.

In a study conducted by Kote-Jarai et al., on lymphocyte cultures in vitro from 5 unaffected BRCA1 heterozygous gene mutation carriers and 5 healthy age-matched control women with no individual or family history of cancer, they found that by putting the cell cultures under irradiation with 8 Gray (Gy) at a high dose rate for six days, there were an increased level of chromosomal aberrations in heterozygous BRCA1 mutation carriers compared with controls ($p = 0.0001$). [14]

Egloff et al. published results of a retrospective study carried out at the Mayo Clinic (Minnesota) between 2000 and 2013 on ovarian, fallopian tube, or primary peritoneal cancer patients reporting no differences in the number of hospitalizations during chemotherapy (for various reasons including neutropenia or fever) between 23 BRCA mutation carriers and 59 wild type patients. [15]

However in a similar study conducted in Gliwice in Pauline between 2007 and 2013, Agnieszka Badora-Rybicka et al. analyzed 172 patients with newly diagnosed epithelial OC, who received combined platinum-taxane chemotherapy. Ninety-six of these patients have known BRCA mutational status with 21 patients being BRCA1 (+) and 75 BRCA1 (−).

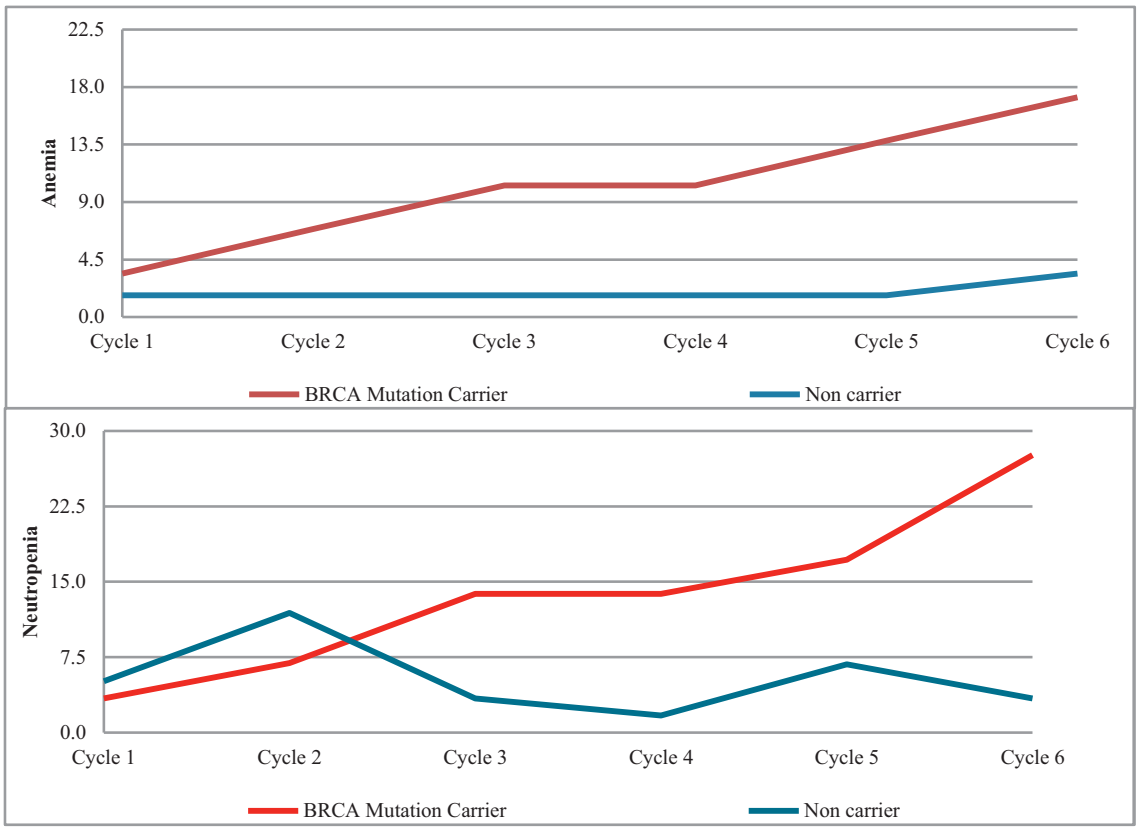

Fig. 1. Rates of anemia and neutropenia per cycle among OC patients underwent chemotherapy, according to BRCA mutational status.

In this study, the authors found that grade 3–4 hematological adverse events were significantly more common among BRCA1 (+) patients (OR = 3.86; 95% CI: 1.14–13.23; $p = 0.02$). [16]

A recent retrospective study by J. Kotsopoulos et al. conducted in Ontario between January 2000 and December 2015, included 130 BRCA mutation carriers and 302 noncarriers patients who received first-line platinum-based chemotherapy. They found no significant difference in 3 measures of hematologic toxicity (neutropenia, anemia, or thrombocytopenia) based on BRCA mutational status across each chemotherapy cycle ($p = 0.06$), but across their entire treatment period, women with a BRCA mutation were more likely to experience at least 1 episode of an absolute neutrophil count of <1.0 × 109/L (34% vs 24%; $p = 0.02$). [12]

These results are reassuring for the maintenance of integrity of dosing regimens, leading the authors to exclude the hypothesis that a haploinsufficiency phenotype exists with respect to the repair of chemotherapy-induced double-strand DNA breaks in this high-risk population. Although our study has fewer patients than Kotsopoulos et al., our results show greater hematological toxicity according to BRCA mutational status. In our analysis we observed at least one episode of granulocyte-colony stimulating growth factors injection and dose delay more frequently in BRCA mutated patients.

The most important indication about the use of these growth factors in most of international and national guidelines is the maintenance of the treatment schedule in curative settings [17,18].

However, although growth factor use was more frequent also when we calculated its rate per events throughout the entire treatment period, dose delay showed a trend but was not statistically significantly different comparing BRCA mutated versus wild type patients.

This data is probably related to the fact that the impact in terms of dose delay of a specific toxic adverse event is usually confined to its first occurrence, thus being scaled back by an adequate management.

Moreover, the absence of grade III–IV anemia, potentially due to a good supportive care and martial implementation, to a higher rate of neutropenia that was largely treated through the use of growth factors and to the rate of thrombocytopenia that was less frequent in both groups, with no significant differences in terms of frequency comparing the two groups may justify the lost of statistical significance of dose delay in these patients.

Of note, since most of international literature stressed the negative impact on prognosis associated to eryhtropoietic growth factors we already abandoned its use by many years for the treatment and prevention of chemotherapy induced anemia.

Finally, comparing results between the randomized phase 2 study conducted by Ledermann et al., to evaluate maintenance treatment with olaparib in platinum sensitive, relapsed, high-grade serous OC patients with or without BRCA1 or BRCA2 germline mutations [19] and those reported by Pujade-Lauraine et al., in their phase 3 trial enrolling only BRCA1/2 mutation carriers with the purpose to confirm the efficacy

Table 3
Hematological toxicity calculated per events throughout the entire treatment period, according to BRCA mutational status.

Toxicity	BRCA1/2 mutated Total events in 348 cycles (%)	BRCA1/2 wild-type Total events in 708 cycles (%)	*p*-Value
Platelets <150 × 10^9/L	20 (5.75%)	10 (1.41%)	<**0.001**
Hemoglobin <100 g/L	36 (10.34%)	14 (1.98%)	<**0.001**
Absolute neutrophil count <1.5 × 10^9/L	92 (26.44%)	50 (7.06%)	<**0.001**
G-CSFs injection	42 (12.07%)	10 (1.41%)	<**0.001**
Dose reduction	30 (8.62%)	38 (5.37%)	0.22
Dose delay	66 (18.96%)	70 (9.89%)	0.08

p-Value was estimated using a Chi-square Pearson's test.
G-CSFs, granulocyte-colony stimulating growth factors.

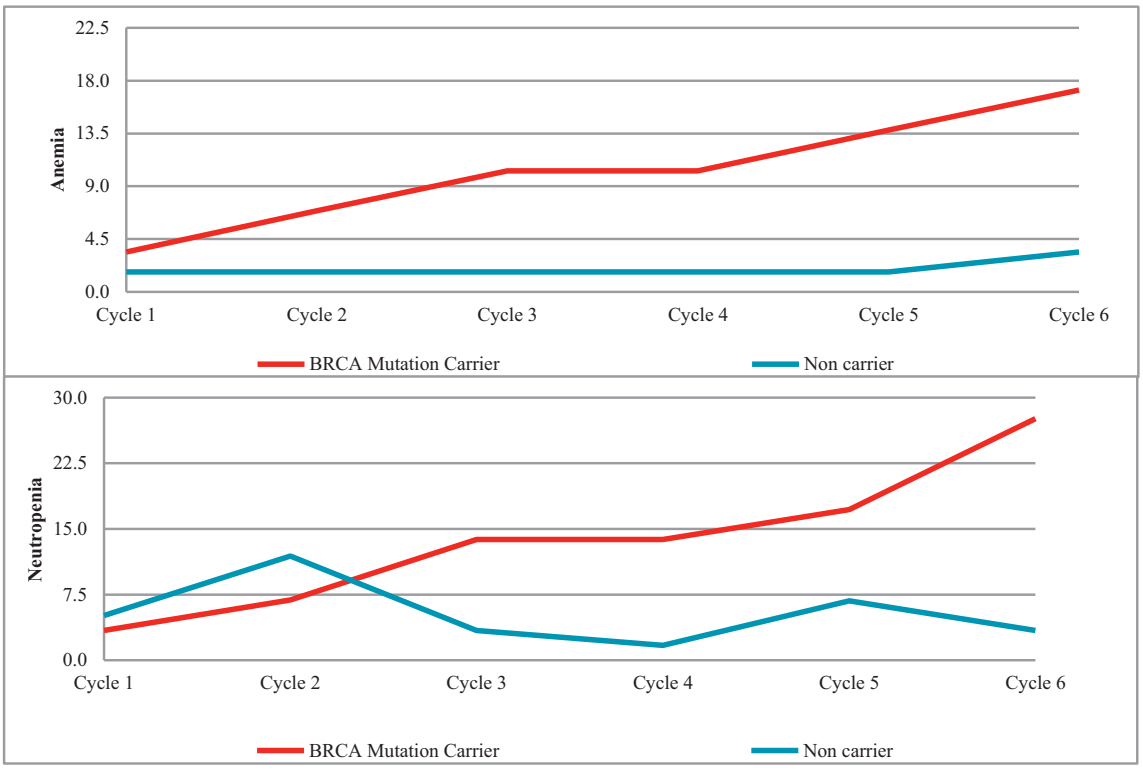

Fig. 2. Rates of anemia and neutropenia in NACT patients per cycle, according to BRCA mutational status.

of Olaparib in these patients, the hematologic toxicity profile is highest in the second trial. [20]

This data might support the hypothesis suggesting the major hematologic toxicity profile in BRCA mutated patients and induce clinicians to better define the dosage of chemotherapy such as strategies of monitoring and follow-up of ovarian cancer patients with BRCA1-2 mutations during treatment.

Our analysis suffers from the same limitations of any other retrospective study and its same nature might justify discordant results reported in international literature.

Thus, we strongly believe in the importance to design future studies in order to prospectively evaluate the potential effects of platinum-based chemotherapy on these patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contribution

Federica Tomao Study design, Drafting of the manuscript, Statistical analysis and Interpretation of data.

Lucia Musacchio Acquisition of data, Drafting of the manuscript.

Federica Di Mauro Acquisition of data, Contribution to statistical analysis, Drafting of the manuscript.

Serena Maria Boccia Acquisition of data, Drafting of the manuscript.

Violante Di Donato Contribution to statistical analysis and Interpretation of data, Critical revision of the manuscript for important intellectual content.

Antonella Giancotti Critical revision of the manuscript for important intellectual content.

Giorgia Perniola Critical revision of the manuscript for important intellectual content.

Innocenza Palaia Critical revision of the manuscript for important intellectual content.

Ludovico Muzii Critical revision of the manuscript for important intellectual content.

Pierluigi Benedetti Panici Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.04.009.

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