Effects of neoadjuvant chemotherapy in ovarian cancer patients with different germline BRCA1/2 mutational status: A retrospective study

Mengdi Fu

Shandong University Qilu Hospital

Chengjuan Jin

Shandong University Qilu Hospital

Jingying Chen

Shandong University Qilu Hospital

Shuai Feng

Shandong Cancer Hospital: Shandong Cancer Hospital and Institute

Lekai Nie

Qilu Hospital of Shandong University Qingdao

Yang Zhang

Shandong University Qilu Hospital

Jin Peng

Shandong University Qilu Hospital

Xia Wang

Shandong University Qilu Hospital

Hualei Bu

Shandong University Qilu Hospital

Beihua Kong (✉ kongbeihua@126.com)

Shandong University Qilu Hospital

Research

Keywords: Neoadjuvant chemotherapy, primary debulking surgery, BRCA, prognosis

Posted Date: August 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-786505/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Frontiers in Oncology on January 6th, 2022. See the published version at <https://doi.org/10.3389/fonc.2021.810099>.

Abstract

Background

Whether neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) against primary debulking surgery (PDS) has a differential effect on prognosis due to Breast Cancer Susceptibility Genes (BRCA)1/2 mutations has not been confirmed by current studies.

Methods

All patients included in this retrospective study were admitted to Qilu Hospital of Shandong University between January 2009 and June 2020, and germline BRCA1/2 mutation were tested. Patients in stage IIIB, IIIC, and IV, re-staged by International Federation of Gynecology and Obstetrics (FIGO) 2014, were selected for analysis. All patients with NAC received 1–3 cycles of platinum-containing (carboplatin, cisplatin, or nedaplatin) chemotherapy. Patients who received maintenance therapy after chemotherapy were not eligible for this study. All relevant medical records were collected.

Results

A total of 308 patients were enrolled in the study, including 108 patients with BRCA1/2 mutations (BRCAmut), and 200 patients with BRCA1/2 wild-type (BRCAwt). In the two groups, 36 BRCAmut patients (33.3%) and 59 BRCAwt patients (29.5%) received neoadjuvant chemotherapy. The progression-free survival (PFS) of BRCAmut patients was significantly reduced after NAC (median: 15.0 vs. 19.0 months, HR = 0.59; $p = 0.03$); however, there was no statistical difference in overall survival (OS) (median: 75.1 vs. 68.5 months, HR = 0.90; $p = 0.72$). Whether BRCAwt patients received NAC had no significant effect on PFS (median: 13.5 vs. 14.6 months, HR = 1.02; $p = 0.90$) or OS (median: 54.0 vs. 56.4 months, HR = 1.23; $p = 0.34$). Multivariate analyses showed that the independent predictors of prolonged survival were PDS ($p = 0.003$), the absence of residual tumor after surgery ($p = 0.010$), and FIGO III stage ($p = 0.011$).

Conclusions

For advanced-stage ovarian cancer patients treated with NAC followed by IDS, PFS and OS were not significantly affected in BRCAwt patients. In BRCAmut patients, NAC-IDS resulted in a shortened PFS, but had no further effect on overall survival.

Background

Ovarian cancer is the most lethal gynecological malignancy. According to the 2021 Cancer Statistics Report published by the American Cancer Society, there will be an estimated 21,410 new ovarian cancer cases and 13,770 deaths in the United States in 2021[1]. Ovarian cancer has no typical clinical symptoms

in its early stage, and there is no effective screening method; therefore, the vast majority of patients have reached the advanced stage at diagnosis, leading to poor prognoses[2]. For patients with FIGO stage III/IV, the maximum cytoreductive surgery (R1, residual lesions less than 1 cm; R0, no residual lesions) is the most critical factor affecting the prognosis[3–5]; however, if it is difficult to remove metastatic lesions in the intestine, spleen, liver or abdominal para-aortic lymph nodes due to extensive tumor metastasis, not all patients can achieve satisfactory resection from primary debulking surgery (PDS). Therefore, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) can be used as an alternative treatment to achieve maximum resection of lesions. To date, several clinical trials have confirmed that there was no significant difference between NAC-IDS and PDS in the prognoses of ovarian cancer patients[6–8].

The discovery of the BRCA1/2 mutations is one of the milestones in the treatment of ovarian cancer. Ovarian cancer patients with BRCA1/2 mutations (BRCAmut), compared with BRCA1/2 wild-type (BRCAwt) patients, have a higher efficacy of platinum-based chemotherapy, a longer recurrence interval due to the presence of homologous recombination defects, and maintain a higher response rate to platinum-based chemotherapy after recurrence[9, 10]. In addition, based on the synthetic lethal theory of poly (ADP-ribose) polymerase inhibitor (PARPi), BRCAmut patients have significantly prolonged survival in salvage therapy and maintenance therapy with PARPi[11, 12]. Thus, the treatment of ovarian cancer patients can be divided into two groups based on the mutational status of BRCA1/2. Whether NAC followed by IDS has a differential effect on prognosis due to BRCA1/2 mutations has not been confirmed by current studies; therefore, we conducted this retrospective study to explore the effect of BRCA1/2 mutations on neoadjuvant chemotherapy.

Methods

Patients and clinical data

All patients included in this retrospective study were admitted to Qilu Hospital of Shandong University between January 2009 and June 2020. A flowchart of this study is presented in Fig. 1. Patients were re-staged according to FIGO2014, and patients in stage IIIB, IIIC, and IV were selected for analysis. All patients with NAC received 1–3 cycles of platinum-containing (carboplatin, cisplatin, or nedaplatin) chemotherapy. Patients who received only one cycle of NAC were eligible only if the sum of lesions decreased by more than 30% according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[13]. Patients who received maintenance therapy after chemotherapy, such as PARP inhibitors or bevacizumab, were not eligible for this study. The determination of response and progression-free survival (PFS) were in accordance with RECIST criteria; if the data for the RECIST criteria were not complete, CA-125 level was used as an alternative, only if the pretreatment level was at least twice the upper limit of normal[13].

Relevant medical data collected from patients included: age, the serum cancer antigen (CA) 125 level at diagnosis, maximum diameter of primary lesion, regimens and cycles of NAC, changes of the maximum

diameter of primary lesions and sum of target lesions based on RECIST standard after NAC, hematological toxicity of NAC based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0, operative duration, hemorrhage volume, residual lesions, pathological types, postoperative chemotherapy regimens, cycles and hematological toxicity, history of PARP inhibitors, FPS and OS.

Germline BRCA1/2 testing

The BRCA1/2 genetic testing panels used for detection covered the entire coding sequences of the BRCA1 and BRCA2 gene, including 10–50 bases of adjacent intronic sequences of each exon. Sequencing was performed on next generation sequence (NGS) platform according to Illumina's protocol. Sanger DNA sequencing using specific gene primers was performed to confirm each reported variant. Multiplex ligation-dependent probe amplification was used to detect BRCA 1/2 large fragment rearrangements. The variants of the mutations were classified according to the 5-class classification standard[14].

Statistical methods

Student's t-test was used to compare the differences in continuous variables. The chi-square test was performed to analyze differences in clinical characteristics. PFS and OS analyses were performed by Kaplan-Meier method. Multivariate proportional odds models were used to identify variables associated with PFS outcome of BRCAmut group, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. All statistical analyses were performed by Prism 8 version 8.4.0. Significance levels were * $p < 0.05$, ** $p < 0.01$.

Results

Characteristics of the Patients and Treatment Received

Between January 2009 and June 2020, 705 ovarian cancer patients underwent germinal BRCA1/2 gene test. There were 308 patients enrolled in the study, including 108 BRCAmut patients and 200 BRCAwt patients. In the two groups, 36 patients (33.3%) and 59 patients (29.5%) received NAC, respectively, with no statistical difference ($p = 0.49$). All patients received carboplatin, cisplatin, or nedaplatin based chemotherapy. The chemotherapy regimens and NAC cycles are shown in Table 1.

Table 1
Chemotherapy regimens of Patients.

Characteristic	BRCAmut	BRCAwT
Chemotherapy regimens of NAC		
Carboplatin based	23 (63.9%)	24 (40.7%)
Cisplatin based	10 (27.8%)	23 (39.0%)
Nedaplatin based	1 (2.8%)	2 (3.4%)
Multiple platinum	2 (5.6%)	8 (13.6%)
Unknown	0 (0%)	2 (3.4%)
Cycle of NAC		
1	6 (16.7%)	10 (16.9%)
2	18 (50.0%)	28 (47.5%)
3	12 (33.3%)	21 (35.6%)
Chemotherapy regimens after surgery of NAC-IDS		
Carboplatin based	23 (63.9%)	25 (42.4%)
Cisplatin based	5 (13.9%)	13 (22.0%)
Nedaplatin based	1 (2.8%)	7 (11.9%)
Multiple platinum	7 (19.4%)	12 (20.3%)
Unknown	0 (0%)	2 (3.4%)
Chemotherapy regimens after surgery of PDS		
Carboplatin based	37 (51.4%)	77 (54.6%)
Cisplatin based	15 (20.8%)	25 (17.7%)
Nedaplatin based	3 (4.2%)	4 (2.8%)
Multiple platinum	15 (20.8%)	32 (22.7%)
Unknown	2 (2.8%)	3 (2.1%)

The characteristics of the patients were shown in Tables 2 and 3. Among BRCAmut patients receiving NAC-IDS and PDS, the median ages at diagnosis were 53 years (range: 34–71) and 52 years (range: 34–79), respectively, with no significant difference. The pathological types of patients in both groups were mainly high-grade serous carcinoma (91.7% and 94.4%, respectively), and the proportion of the maximum volume of primary lesions at diagnosis was similar. The proportion of CA125 above 1000U/ml in patients with NAC was higher than patients with PDS (58.3% vs. 30.6%, $p = 0.002$). After receiving NAC, the largest

primary lesions in 75.0% of patients were reduced to less than 5cm; before chemotherapy, the proportion was only 13.9%. The operative time of patients in the two groups were similar, with a median of 155min (range: 80-370min) and 155min (range: 75-600min), respectively. However, the amount of blood loss in patients receiving NAC was significantly reduced than patients with PDS (300, range 100-1000ml vs. 400, rang 100-2000ml; $p = 0.044$). Moreover, NAC significantly increased the proportion of R0 excisions (55.5% vs. 27.8%; $p = 0.004$). For adverse reactions, the most common hematologic toxicities (CTCAE ≥ 3) were neutrophil count decreased and white blood cell count decreased, which were 22.2% and 19.4% in the neoadjuvant patients. The proportion of postoperative hematologic toxicities in the two groups was similar ($p = 0.644$). In addition, it is worth noting that 52% of BRCAmut patients were treated with PARP inhibitors in the posterior lines of treatment.

Table 2
Baseline Characteristics of the BRCAmut Patients.

Characteristic	Neoadjuvant Chemotherapy (N = 36)	Primary Debulking Surgery (N = 72)	P value
Age (years)			
Median	53	52	0.878
Range	34–71	34–79	
Histologic type – no. (%)			
High-grade serous	33 (91.7%)	68 (94.4%)	NA
Low-grade serous	0 (0%)	1 (1.4%)	
Serous not specified	1 (2.8%)	3 (4.2%)	
Mucinous	0 (0%)	0 (0%)	
Clear-cell	2 (5.6%)	0 (0%)	
Endometrioid	0 (0%)	0 (0%)	
Mixed	0 (0%)	0 (0%)	
Stage – no. (%)			
IIIB/IIIC	32 (88.9%)	62 (86.1%)	0.685
IVa/IVb	4 (11.1%)	10 (13.9%)	
Largest primary tumor at diagnosed (cm) – no. (%)			
≤ 5	5 (13.9%)	11 (15.3%)	0.829
> 5, ≤ 10	18 (50.0%)	38 (52.8%)	
> 10, ≤ 15	4 (11.1%)	14 (19.4%)	
> 15	1 (2.8%)	4 (5.6%)	
Unknown	8 (22.2)	5 (6.9%)	
Largest primary tumor before surgery (cm) – no. (%)			
≤ 5	27 (75.0%)	NA	NA
> 5, ≤ 10	8 (22.2%)	NA	
> 10, ≤ 15	0 (0%)	NA	

Characteristic	Neoadjuvant Chemotherapy (N = 36)	Primary Debulking Surgery (N = 72)	P value
> 15	0 (0%)	NA	
Unknown	1 (2.8%)	NA	
Serum CA-125(U/ml)			
≤ 1000	8 (22.2%)	36 (50.0%)	0.002**
> 1000	21 (58.3%)	22 (30.6%)	
Unknown	7 (19.4%)	14 (19.4%)	
Residual lesions (cm)			
0	20 (55.5%)	20 (27.8%)	0.004**
< 1	6 (16.7%)	33 (45.8%)	
≥ 1	7 (19.4%)	17 (23.6%)	
Unknown	3 (8.3%)	2 (2.8%)	
Duration of Operation(min)			
Median	155	155	0.344
Range	80–370	75–600	
Hemorrhage of Operation (ml)			
Media	300	400	0.044*
Range	100–1000	100–2000	
Response of NAC			
PR/CR	21 (58.3%)	NA	
SD/PD	7 (19.4%)	NA	
Unknown	8 (22.2%)	NA	
History of PARPi			
Yes	20 (55.6%)	42 (58.3%)	0.783
No/Unknown	16 (44.4%)	30 (41.7%)	
Hematologic toxicity of NAC (≥ 3 CTCAE)			

Characteristic	Neoadjuvant Chemotherapy (N = 36)	Primary Debulking Surgery (N = 72)	P value
White blood cell decreased	7 (19.4%)	NA	NA
Neutrophil decreased	8 (22.2%)	NA	
Anemia	1 (2.8%)	NA	
Platelet decreased	1 (2.8%)	NA	
Hematologic toxicity after surgery ($\geq$ 3 CTCAE)			
White blood cell decreased	7 (19.4%)	11 (15.3%)	0.644
Neutrophil decreased	10 (27.8%)	27 (37.5%)	
Anemia	3 (8.3%)	3 (4.2%)	
Platelet decreased	1 (2.8%)	2 (2.8%)	

Table 3
Baseline Characteristics of the BRCAwt Patients.

Characteristic	Neoadjuvant Chemotherapy (N = 59)	Primary Debulking Surgery (N = 141)	P value
Age (years)			
Median	56	53	0.107
Range	23–75	26–73	
Histologic type – no. (%)			
High-grade serous	53 (89.8%)	120 (85.1%)	NA
Low-grade serous	2 (3.4%)	5 (3.5%)	
Serous not specified	3 (5.1%)	3 (2.1%)	
Mucinous	0 (0%)	4 (2.8%)	
Clear-cell	1 (1.7%)	3 (2.1%)	
Endometrioid	0 (0%)	5 (3.5%)	
Mixed	0 (0%)	1 (0.7%)	
Stage – no. (%)			
IIIB/IIIC	50 (84.7%)	131 (92.9%)	0.073
IVa/IVb	9 (15.3%)	10 (7.1%)	
Largest tumor at diagnosed (cm) – no. (%)			
≤ 5	7 (11.9%)	23 (16.3%)	0.962
> 5, ≤ 10	27 (45.8%)	69 (48.9%)	
> 10, ≤ 15	12 (20.3%)	32 (22.7%)	
> 15	3 (5.1%)	9 (6.4%)	
Unknown	10 (16.9%)	8 (5.7%)	
Largest tumor before surgery (cm) – no. (%)			
≤ 5	36 (61.0%)	NA	NA
> 5, ≤ 10	13 (22.0%)	NA	
> 10, ≤ 15	4 (6.8%)	NA	

Characteristic	Neoadjuvant Chemotherapy (N = 59)	Primary Debulking Surgery (N = 141)	P value
> 15	2 (3.4%)	NA	
Unknown	4 (6.8%)	NA	
Serum CA-125(U/ml)			
≤ 1000	18 (30.5%)	76 (53.9%)	0.019*
> 1000	26 (44.1%)	48 (34.0%)	
Unknown	15 (25.4%)	17 (12.1%)	
Residual lesions (cm)			
0	25 (42.4%)	40 (28.4%)	0.034*
≤ 1	23 (39.0%)	56 (39.7%)	
> 1	7 (11.9%)	38 (27.0%)	
Unknown	4 (6.8%)	7 (5.0%)	
Duration of Operation(min)			
Median	145	155	0.758
Range	70–600	75–550	
Hemorrhage of Operation (ml)			
Media	300	400	0.019*
Range	60-1500	100–6000	
Response of NAC			
PR/CR	24 (40.7%)	NA	
SD/PD	24 (40.7%)	NA	
Unknown	11 (18.6%)	NA	
Hematologic toxicity of NAC (≥ 3 CTCAE)			
White blood cell decreased	5 (8.5%)	NA	NA
Neutrophil decreased	9 (15.3%)	NA	
Anemia	4 (6.8%)	NA	

Characteristic	Neoadjuvant Chemotherapy (N = 59)	Primary Debulking Surgery (N = 141)	P value
Platelet decreased	0 (0%)	NA	
Hematologic toxicity after surgery (≥ 3 CTCAE)			
White blood cell decreased	7 (11.9%)	27 (19.1%)	0.858
Neutrophil decreased	11 (18.6%)	42 (29.8%)	
Anemia	2 (3.4%)	4 (2.8%)	
Platelet decreased	1 (1.7%)	2 (1.4%)	

The median age at diagnosis was slightly higher in BRCAwt patients in both NAC-IDS and PDS group (56 and 53 years, respectively) compared to BRCAmut patients. The pathological type was dominated by high-grade serous carcinoma, and the proportion was similar between NAC-IDS and PDS groups. The proportion of FIGO stage III patients (84.7% vs. 92.9%, $p = 0.073$) and surgical duration (median 145 vs. 155 min, $p = 0.758$) were also similar between the two groups. There was no statistical difference in the proportion of the largest primary lesion. As in BRCAmut patients, the proportion of BRCAwt patients receiving NAC with ca125 level above 1000u/ml (44.1% vs. 34.0%; $p = 0.019$) and the R0 resection rate (42.4% vs. 28.4%; $p = 0.034$) were higher than those in PDS patients; however, the blood loss was significantly reduced (median 300 ml, range 60-1500ml vs. median 400ml, range 100-6000ml; $p = 0.019$). The hematologic toxicity of NAC in BRCAwt patients was similar to that of BRCAmut, and there was no statistical difference in postoperative hematologic toxicity between NAC-IDS and PDS group ($p = 0.858$). Finally, BRCAwt patients did not respond as significantly to NAC as BRCAmut; among the evaluable patients, the ratios of partial response (PR) were 50.0% (24/48) and 75.0% (21/28), respectively ($p = 0.03$).

Effect of neoadjuvant chemotherapy on PFS and OS

Regardless of the BRCA1/2 mutational status, there were no statistical differences in prognoses between patients in the NAC-IDS and PDS groups for PFS, (median: 15.4 vs. 14.9 months, HR = 0.84; $p = 0.19$) (Fig. 2A) or OS (median: 57.1 vs. 64.7 months, HR = 1.11; $p = 0.56$) (Fig. 3A). Further analysis found that the PFS of BRCAmut patients was significantly reduced after NAC (median, 15.0 vs. 19.0months, HR = 0.59; $p = 0.03$) (Fig. 2B); however, there was no statistical difference in OS (median, 75.1 vs. 68.5months, HR = 0.90; $p = 0.72$) (Fig. 3B). Whether BRCAwt patients received NAC had no significant effect on PFS (median, 13.5 vs. 14.6 months, HR = 1.02; $p = 0.90$) (Fig. 2C) and OS (median, 54.0 vs. 56.4 months, HR = 1.23; $p = 0.34$) (Fig. 3C).

Cox regression multivariate analyses were performed, with PFS as the endpoint, and included the following variables: age at diagnosis, residual lesions, largest primary tumor size, FIGO stage, NAC-IDS or

not, and CA-125 level. The strongest independent predictors of prolonged survival, in descending order PDS ($p = 0.003$), were the absence of residual tumor after surgery ($p = 0.010$) and FIGO III disease ($p = 0.011$). The other variables did not significantly influence PFS (Table 4).

Table 4
Multivariate analysis of prognostic markers related to PFS in BRCAmut patients

Item	PFS	
	HR(95% CI)	p-value
FIGO (III / IV)	0.397(0.194–0.811)	0.011*
NAC-IDS (No / Yes)	0.393(0.211–0.732)	0.003**
Residual Lesions(R0 / R1 + R2)	0.490(0.285–0.840)	0.010*
CA-125 (≤ 1000 / >1000 U/ml)	0.794(0.464–1.359)	0.401
Age(≤ 50 / >50 years)	0.887 (0.522–1.507)	0.887
Maximum of Lesions (≤ 10 / >10 cm)	0.636(0.345–1.171)	0.146

Discussion

In this retrospective study, we found that without considering the BRCA1/2 mutation status, both PFS and OS after neoadjuvant chemotherapy followed by interval debulking surgery were similar to survivals with primary surgery followed by chemotherapy, which was consistent with the conclusions of previous randomized controlled trials[8, 15]. In BRCAmut patients, NAC-IDS significantly shortened PFS, however, it had no effect on OS. For BRCAwt patients, NAC did not significantly affect the prognosis. To our knowledge, this is the first retrospective study to date to discuss the effect of NAC on prognosis based on the BRCA mutational status.

The proportion of patients with BRCA1/2 mutations was 35.1%, which is much higher than that previously reported in the literature[16–18]. This could be related to the fact that all patients included in the study were at an advanced stage. Both BRCA1 and BRCA2 are tumor suppressor genes, and their functional proteins play an important role in DNA homologous recombinant double-stranded break repair. In the absence of functional BRCA1/2 gene, tumor cells are more aggressive and therefore more prone to distant metastasis, leading to an increased proportion of patients with FIGO III and IV stage[19]. According to previous reports, the highest proportion of BRCA1/2 mutation in Chinese ovarian cancer patients was 28.5%. However, if stage III and IV patients were separately counted, the proportion of patients with BRCA1/2 mutation was significantly increased in these studies[16, 18].

The primary evaluation criteria for the initial treatment of advanced ovarian cancer patients is whether satisfactory cytoreductive surgery can be achieved in PDS, especially R0 resection, which could

significantly prolong survival[20]. At present, clinical practice guidelines and expert consensus suggest that NAC is recommended for FIGO stage III to IV patients with poor physical status and unable to tolerate surgery, and for patients in whom it is difficult to achieve satisfactory tumor cytoreductive surgery (R0 and R1)[20–22]. Several studies have confirmed that the serum CA-125 level was an important predictor of surgical outcome, defined as successful cytoreductive surgery with a residual tumor ≤ 1 cm, and is a significant factor in decision-making regarding the proper selection for PDS or NAC[23–25]. In our study, the largest primary lesion at diagnosis was similar in both the NAC and PDS groups regardless of BRCA mutation, but the CA-125 levels in patients receiving NAC were significantly higher than those in the PDS group, which is one of the important reasons for choosing NAC. In addition, NAC can significantly increase the proportion of R0 resection and reduce the amount of bleeding during surgery, consistent with the conclusions of previous reports[6, 15].

Although R0 resection rates were significantly improved in both BRCAmut and BRCAwt patients receiving NAC, the OS did not improve, nor did PFS in BRCAwt patients. In contrast, in BRCAmut patients, NAC significantly shortened PFS; further multivariate analysis found that NAC-IDS, FIGO IV stage, and R1/R2 resection were risk factors for poor PFS. Compared with BRCAwt patients, BRCAmut patients previously showed a significantly increased peritoneal tumor load[26], were associated with nodular peritoneal disease pattern[27], and showed increased sensitivity to NAC[28]. In our study, the proportion of BRCAmut patients who achieved partial response after neoadjuvant chemotherapy was 75.0%, which was significantly higher than that of BRCAwt patients (50%). The above reasons could cause more peritoneal lesions to become invisible after NAC and, thus, cannot be completely resected; therefore, R0 resection may not be truly achieved; instead, the complete response (CR) status was achieved through chemotherapy, which may be the main reason for reduced PFS in BRCAmut patients.

BRCA1/2 genes are tumor suppressors, that play an important role in DNA damage repair and normal cell growth. BRCA1/2 mutations can inhibit the repair of DNA damage, resulting in homologous recombination deficiency, which eventually lead to carcinogenesis[29]. In BRCA1/2 mutated tumor cells, DNA double-stranded repair function is lost; since PARP inhibitors can block single-stranded DNA repair, this results in a "synthetic lethal" effect that leads to the death of tumor cells[9]. Therefore, PARP inhibitors have excellent maintenance treatment effects in BRCAmut patients, which can significantly prolong the PFS and OS[30, 31]. In the SOLO-2 clinical trial of olaparib[32], maintenance therapy with olaparib in BRCAmut platinum-sensitive relapse patients extended the relapse time by 24.7 months and reduced the risk of recurrence or death by 70%. In addition, the objective response rate in BRCAmut patients with platinum-sensitive relapses above three lines was about 70% when treated with PARP inhibitors[12]. The evaluation of PFS in our study, although excluding patients with PARP inhibitors for maintenance therapy, there were a large number of patients treated with PARP inhibitors in the posterior line of treatment. This is probably the main reason for the subsequent overall survival consistency.

This retrospective study had several limitations. First, several studies have suggested that surgery is appropriate after three cycles of NAC[6, 8, 21]. Patients with 1–3 cycles were included in our study; however, patients with one cycle of chemotherapy, were not suitable if PR was not achieved, which may

affect the prognosis to some extent. In addition, we did not collect details of patients using PARP inhibitors in the posterior line; therefore, no further analysis of OS was performed to exclude the effect of PARP inhibitors.

Conclusion

In conclusion, for advanced-stage ovarian cancer patients treated with NAC followed by IDS, PFS and OS were not significantly affected in BRCAwt patients. In BRCAmut patients, NAC-IDS resulted in a shortened PFS, but had no further effect on OS. Additional randomized controlled trials will be necessary to elucidate the effect of BRCA1/2 mutation on prognoses of advanced-stage ovarian cancer patients.

Abbreviations

NAC: Neoadjuvant chemotherapy; IDS: Interval debulking surgery; PDS: Primary debulking surgery; BRCA: Breast Cancer Susceptibility Genes; FIGO: International Federation of Gynecology and Obstetrics; PFS: Progression-free survival; OS: Overall survival; PAPR: Poly (ADP-ribose) polymerase; RECIST: Response evaluation criteria in solid tumors; NGS: Next generation sequence; HR: Hazard ratios; CI: Confidence intervals; CA125: cancer antigen 125; CTCAE: Common Terminology Criteria for Adverse Events.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Qilu Hospital of Shandong University, and informed consents were obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Department of Science Technology of Jinan city (No. 201705051).

Authors' contributions

Mengdi Fu: Conceptualization, investigation, methodology, project administration, and writing-original draft. Chengjuan Jin: Data curation, formal analysis, and software. Jingying Chen, Shuai Feng, Lekai Nie, Xia Wang, and Yang Zhang: Data curation. Jin Peng: Funding acquisition, investigation and methodology. Hualei Bu and Beihua Kong: Formal analysis, methodology, supervision, validation, review, and editing. All authors have reviewed and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics. 2021. *CA Cancer J Clin.* 2021;71:7–33.
2. Paik ES, Lee YY, Lee EJ, Choi CH, Kim TJ, Lee JW, et al. Survival analysis of revised 2013 FIGO staging classification of epithelial ovarian cancer and comparison with previous FIGO staging classification. *Obstet Gynecol Sci.* 2015;58:124–34.
3. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer.* 2009;115:1234–44.
4. Kotsopoulos J, Rosen B, Fan I, Moody J, McLaughlin JR, Risch H, et al. Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. *Gynecol Oncol.* 2016;140:42–7.
5. Chi DS, Eisenhauer EL, Lang J, Huh J, Haddad L, Abu-Rustum NR, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? *Gynecol Oncol.* 2006;103:559–64.
6. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363:943–53.
7. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet.* 2015;386:249–57.
8. Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. *Eur J Cancer.* 2016;64:22–31.
9. Tan DS, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with

- epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol*. 2008;26:5530–6.
10. Safra T, Lai WC, Borgato L, Nicoletto MO, Berman T, Reich E, et al. BRCA mutations and outcome in epithelial ovarian cancer (EOC): experience in ethnically diverse groups. *Ann Oncol*. 2013;24(Suppl 8):viii63–8.
  11. Ison G, Howie LJ, Amiri-Kordestani L, Zhang L, Tang S, Sridhara R, et al. FDA Approval Summary: Niraparib for the Maintenance Treatment of Patients with Recurrent Ovarian Cancer in Response to Platinum-Based Chemotherapy. *Clin Cancer Res*. 2018;24:4066–71.
  12. Li N, Bu H, Liu J, Zhu J, Zhou Q, Wang L, et al. An Open-label, Multicenter, Single-arm, Phase II Study of Fluzoparib in Patients with Germline BRCA1/2 Mutation and Platinum-sensitive Recurrent Ovarian Cancer. *Clin Cancer Res*. 2021;27:2452–8.
  13. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIg). *Int J Gynecol Cancer*. 2011;21:419–23.
  14. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat*. 2008;29:1282–91.
  15. Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59:22–33.
  16. Bu H, Chen J, Li Q, Hou J, Wei Y, Yang X, et al. BRCA mutation frequency and clinical features of ovarian cancer patients: A report from a Chinese study group. *J Obstet Gynaecol Res*. 2019;45:2267–74.
  17. Wu X, Wu L, Kong B, Liu J, Yin R, Wen H, et al. The First Nationwide Multicenter Prevalence Study of Germline BRCA1 and BRCA2 Mutations in Chinese Ovarian Cancer Patients. *Int J Gynecol Cancer*. 2017;27:1650–7.
  18. Shi T, Wang P, Xie C, Yin S, Shi D, Wei C, et al. BRCA1 and BRCA2 mutations in ovarian cancer patients from China: ethnic-related mutations in BRCA1 associated with an increased risk of ovarian cancer. *Int J Cancer*. 2017;140:2051–9.
  19. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA*. 2012;307:382–90.
  20. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30:672–705.

21. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34:3460–73.
22. Suh DH, Chang SJ, Song T, Lee S, Kang WD, Lee SJ, et al. Practice guidelines for management of ovarian cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement. *J Gynecol Oncol*. 2018;29:e56.
23. Arab M, Jamdar F, Sadat Hosseini M, Ghodssi- Ghasemabadi R, Farzaneh F, Ashrafganjoei T. Model for Prediction of Optimal Debulking of Epithelial Ovarian Cancer. *Asian Pac J Cancer Prev*. 2018;19:1319–24.
24. Saygili U, Guclu S, Uslu T, Erten O, Demir N, Onvural A. Can serum CA-125 levels predict the optimal primary cytoreduction in patients with advanced ovarian carcinoma? *Gynecol Oncol*. 2002;86:57–61.
25. Gerner O, Lurian M, Gdalevich M, Kapustian V, Piura E, Schneider D, et al. A multicenter study of CA 125 level as a predictor of non-optimal primary cytoreduction of advanced epithelial ovarian cancer. *Eur J Surg Oncol*. 2005;31:1006–10.
26. Petrillo M, Marchetti C, De Leo R, Musella A, Capoluongo E, Paris I, et al. BRCA mutational status, initial disease presentation, and clinical outcome in high-grade serous advanced ovarian cancer: a multicenter study. *Am J Obstet Gynecol*. 2017;217:334. e1- e9.
27. Nougaret S, Lakhman Y, Gonen M, Goldman DA, Micco M, D'Anastasi M, et al. High-Grade Serous Ovarian Cancer: Associations between BRCA Mutation Status, CT Imaging Phenotypes, and Clinical Outcomes. *Radiology*. 2017;285:472–81.
28. Gorodnova TV, Sokolenko AP, Ivantsov AO, Iyevleva AG, Suspitsin EN, Aleksakhina SN, et al. High response rates to neoadjuvant platinum-based therapy in ovarian cancer patients carrying germ-line BRCA mutation. *Cancer Lett*. 2015;369:363–7.
29. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov*. 2015;5:1137–54.
30. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018;379:2495–505.
31. Essel KG, Moore KN. Niraparib for the treatment of ovarian cancer. *Expert Rev Anticancer Ther*. 2018;18:727–33.
32. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1274–84.

Figures

Figure 1

Flowchart

Figure 2

PDS groups for PFS, (median: 15.4 vs. 14.9 months, HR=0.84; p=0.19) (Figure 2A) or OS (median: 57.1 vs. 64.7 months, HR=1.11; p=0.56) (Figure 3A). Further analysis found that the PFS of BRCAmut patients was significantly reduced after NAC (median, 15.0 vs. 19.0 months, HR=0.59; p=0.03) (Figure 2B); however, there was no statistical difference in OS (median, 75.1 vs. 68.5 months, HR=0.90; p=0.72) (Figure 3B). Whether BRCAwt patients received NAC had no significant effect on PFS (median, 13.5 vs. 14.6

months, HR=1.02; p=0.90) (Figure 2C) and OS (median, 54.0 vs. 56.4 months, HR=1.23; p=0.34) (Figure 3C).

Figure 3

PDS groups for PFS, (median: 15.4 vs. 14.9 months, HR=0.84; p=0.19) (Figure 2A) or OS (median: 57.1 vs. 64.7 months, HR=1.11; p=0.56) (Figure 3A). Further analysis found that the PFS of BRCAmut patients was significantly reduced after NAC (median, 15.0 vs. 19.0months, HR=0.59; p=0.03) (Figure 2B);

however, there was no statistical difference in OS (median, 75.1 vs. 68.5 months, HR=0.90; p=0.72) (Figure 3B). Whether BRCAwt patients received NAC had no significant effect on PFS (median, 13.5 vs. 14.6 months, HR=1.02; p=0.90) (Figure 2C) and OS (median, 54.0 vs. 56.4 months, HR=1.23; p=0.34) (Figure 3C).