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Research Article

Real-World TRAE Association between Niraparib and Platinum-Based Chemotherapy

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Abstract

Background: Niraparib has been associated with significantly increased Progression-Free Survival (PFS) among patients with newly diagnosed and recurrent Ovarian Cancer (OC) who have had a response to platinum-based chemotherapy, regardless of BRCA status. Pre-clinical studies showed the anti-tumor mechanisms of PARP inhibitors (PARPi) and platinum have some crossover and overlap in the DNA damage repair pathway; patients who respond to platinum-based chemotherapy are also more likely to be sensitive to PARPi. This real-world study mainly aimed to evaluate whether TRAE (Treatment-Related Adverse Event) between platinum-based chemotherapy and niraparib are also associated.

Methods: Patients received niraparib as maintenance treatment or salvage therapy for advanced ovarian cancer at the First Affiliated Hospital of Gannan Medical University from January 2020 to August 2023 were included. Survival data of niraparib treatment and adverse events occurred during the last platinum-based chemotherapy cycle before starting niraparib treatment and during niraparib treatment are documented. Kaplan-Meier method and Fisher's exact test were used for survival analysis and correlation analysis respectively.

Results:

1. 40 patients treated with niraparib were included in the analysis, including 31 patients treated with niraparib for 1st-line maintenance therapy, 6 patients for PSR (platinum-sensitive recurrence) maintenance therapy, and 3 patients for salvage therapy. The overall median follow-up time was 15.0 months (ranged from 2.2 months to 32.1 months).
2. Overall grade≥3 TRAE (40% *vs.* 70%, p=0.012) including anemia (20% *vs.* 45%, p=0.041) and neutrophil count decreased (17.5% *vs.* 57.5%, p<0.001) was significantly lower during niraparib treatment compared to during chemotherapy.
3. Any grade TRAE (75% *vs.* 100%, p=0.002) including white blood cell count decreased (47.5% *vs.* 87.5%, p<0.001), red blood cell count decreased (57.5% *vs.* 92.5%, p<0.001), anemia (55% *vs.* 87.5%, p<0.001) and neutrophil count decreased (35% *vs.* 85%, p<0.001) were also significantly lower in niraparib treatment group compared with chemotherapy group. No new safety signals were identified.
4. The 24-month PFS rates of 1st-line maintenance, PSR maintenance and salvage therapy was 77%, 82% and 60% respectively. The median PFS was not reached in all three patient populations.

Conclusion: In this real-world practice, we observed that patients with advanced ovarian cancer who experienced any grade and grade ≥ 3 TRAE during chemotherapy were well tolerated when treated with niraparib, particularly the incidence of any grade and grade ≥ 3 anemia, and neutrophil count decreased during niraparib treatment were significantly lower compared with that during chemotherapy.

Keywords: TRAE; Niraparib; Chemotherapy; Ovarian cancer

Introduction

Ovarian cancer is the eighth most common cancer among females. In 2020, 313,959 women worldwide were newly diagnosed with ovarian cancer, and 207,252 women died from the disease [1]. The incidence of ovarian cancer in China is increasing and ranks third among malignant tumors of the female reproductive system, with the highest mortality rate. Currently, there is no effective early screening strategy for ovarian cancer, and the early symptoms are often hidden [2]. Approximately 70% of ovarian cancer patients are diagnosed at an advanced stage, and about 80% of those with advanced stage experience recurrence within 3 years after chemotherapy remission. As the number of treatment lines increases, the platinum-free interval becomes shorter, ultimately leading to platinum resistance. The 5-year survival rate is only 15% to 25% [3,4]. In recent years, targeted therapy research has advanced, shifting the treatment approach for epithelial ovarian cancer from the traditional 'tumor cytoreductive surgery+platinum-based chemotherapy' mode to a 'tumor cytoreductive surgery+platinum-based chemotherapy+long-term disease management mode of maintenance therapy'. PARP inhibitors have emerged as an important means of maintaining ovarian cancer. However, there is currently a lack of data on the correlation between real-world niraparib use and hematologic adverse reactions (TRAE) that occur during platinum-based chemotherapy in ovarian cancer patients. Therefore, our study aims to analyze the real-world association between niraparib and TRAE during platinum-based chemotherapy.

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Materials and Methods

Study population

Ovarian cancer patients who achieved CR/PR after platinum-based chemotherapy, platinum-sensitive recurrent ovarian cancer after platinum-based chemotherapy and multi-line chemotherapy in the First Affiliated Hospital of Gannan Medical University from January 2020 to May 2023 were enrolled in this study. Follow-up ended on August 31, 2023. Baseline data of the patients were collected, including the patient's age, weight, family history, clinical stage of the International Federation of Obstetrics and Gynecology (FIGO), pathological type, presence of other comorbidities before chemotherapy, ECOG score, Frontline platinum-based chemotherapy cycles, number of front-line chemotherapy lines, The last line of chemotherapy regimen prior to treatment with niraparib. The hematologic adverse reactions during chemotherapy, ≥ grade 3 adverse reactions during chemotherapy, the end time of the last platinum-containing chemotherapy, and the response to the last platinum-containing chemotherapy were also recorded. Additionally, the baseline number of platelets and CA125 before niraparib treatment, the improvement of genetic testing, adjuvant therapy, and follow-up after the use of niraparib were documented.

Group standard

Inclusion criteria: (1) Patients over 18 years of age with histologically confirmed advanced epithelial ovarian cancer; (2) Patients with ovarian cancer who have achieved CR/PR with platinum-containing chemotherapy and received niraparib after chemotherapy.

Exclusion criteria: (1) ovarian cancer patients under the age of 18; (2) Patients with ovarian cancer with histologically confirmed malignant tumors of other origins. The duration of follow-up was from initiation of niraparib to disease progression or permanent discontinuation or data collection cut-off.

Assessments

Adverse reactions were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Throughout the treatment period, it is recommended to conduct monthly routine blood tests to record the possible hematologic adverse reactions of the follow-up patients.

Dosing regimen

The initial dose of niraparib is administered on an individualized basis. The initial dose is based on basal body weight and platelet count. Patients with a basal weight >77 kg and/or a basal platelet count > 150,000/μl should take 300 mg daily, and patients with a basal weight <77 kg and/or basal platelet count <150,000/μl should take 200 mg daily. Dose reductions were allowed for drug-related adverse effects (300 mg to 200 mg or 100 mg; 200 mg to 100 mg) or drug interruption.

BRCA detection

Target region capture+high-throughput sequencing.

Statistical methods

SPSS 29.0 software was used for statistical analysis, frequency and percentage descriptions were used for count data, and chi-square test and Fisher exact test were used for correlation analysis.

Results

Patient characteristics

A total of 40 patients diagnosed with ovarian cancer and treated with platinum-based chemotherapy and niraparib were included in this study. The median follow-up time after starting niraparib treatment was 15.0 months (range: 2.2-32.1 months). The median age of the patients was 56 years (range: 24-75 years). There were 6 cases (15%), 31 cases (77.5%) and 3 cases (7.5%) of FIGO stage II, III and IV, respectively. Most patients had serous carcinoma (32 (80%)) and endometrioid carcinoma (4 (10%)). All the patients weighed less than 77 kg and 11 of them had a platelet count less than 150 × 10 ^ 9/L. Twenty-eight individuals underwent BRCA testing, including 5 with BRCA1/2 mutations and 23 with BRCA wild-type. The baseline data of the patients are shown in Table 1.

Safety

Forty patients were included in the analysis. There were 40 cases (100%) and 30 cases (75%) of hematologic adverse reactions of any grade during platinum-based chemotherapy and niraparib treatment, including 35 cases (87.5%) and 19 cases (47.5%) of leucopenia, 37 cases (92.5%) and 23 cases (57.5%) of erythropenia, respectively. The incidences of anemia, thrombocytopenia and neutropenia were 35 (87.5%) *vs.* 22 (55%), 16 (40%) *vs.* 12 (30%), 34 (85%) *vs.* 14 (35%). The P values were 0.012, 0.065, 0.625, 0.041, 1.000 and <0.001, respectively. In the two periods, any grade of hematological adverse reactions including leukopenia, erythropenia, anemia and neutropenia were statistically significant. There were 28 cases (70%) and 16 cases (40%) with grade ≥ 3 hematological adverse reactions, including 12 cases (30%) and 5 cases (12.5%) with grade ≥ 3 leukopenia, and 1 case (2.5%) and 3 cases (7.5%) with grade ≥ 3 erythropenia, respectively. Grade ≥ 3 anemia occurred in 18 cases (45%) versus 8 cases (20%), grade ≥ 3 thrombocytopenia in 6 cases (15%) *vs.* 5 cases (12.5%), grade ≥ 3 neutropenia in 23 cases (57.5%) *vs.* 7 cases (17.5%), P values were: 0.012, 0.065, 0.625, 0.041, 1.000, < 0.001. Grade ≥ 3 hematological adverse reactions including anemia and neutropenia in the two periods were statistically significant. There were 10 cases (25%) and 7 cases (17.5%) of severe hematologic toxicity (grade ≥ 4), respectively (p=0.549). The data are presented in Table 2.

During the use of platinum-based chemotherapy, 40 patients had hematologic adverse effects of any grade and 28 patients had hematologic adverse effects of grade ≥ 3. During niraparib maintenance therapy, adverse events of any grade occurred in 38 patients (95%), and bone marrow suppression of any grade occurred in 30 patients, of whom 16 patients had grade ≥ 3 bone marrow suppression. There were 21 cases (52.5%) of non-hematologic adverse reactions, all of which were grade 1-2, and the most common adverse reactions were fatigue, nausea and Vomiting. No new safety signals were found. The data are presented in Table 3.

Discussion

Platinum-based drugs inhibit tumor cell proliferation by interfering with DNA replication and transcription by binding to DNA [5,6]. BRCA1/2 mutations are also associated with high sensitivity for platinum groups. Patients with BRCA mutations have improved overall response to platinum-based therapy, which is associated with longer survival in patients with BRCA-mutated ovarian cancer [5,7]. PARP enzymes, especially PARP-1 and PARP-2, play a key role in the repair of DNA single-strand breaks. Inhibition of PARP leads to the accumulation of single-strand breaks, leading to the collapse of the replication strand and the accumulation of double-strand breaks, which are usually repaired by homologous recombinases. Ovarian cancers with BRCA1/BRCA2 mutations or other HRDs are particularly sensitive to PARP inhibitors because the accumulation

Table 1: Baseline characteristics in 40 patients. Values are reported as frequency (n [%]) or as mean (range).

Characteristic	Number of patients (percent)	Characteristic	Number of patients (percent)
Median age years(range)	56 (24-75)	Front line chemotherapy cycles	
≤ 59	25 (62.5)	≤ 5	5 (12.5)
>59	15 (37.5)	6-9	34 (85)
Median baseline CA125(range)	10.02 (2.15-59.20)	10	1 (2.5)
Baseline body weight		Clinical response after platinum-based chemotherapy	
≥ 77kg	0	Complete response	36 (90)
<77kg	40(100)	Partial response	1 (2.5)
International FIGO stage		Stable disease	3 (7.5)
II	6 (15)	Platelet count	
III	31 (77.5)	≥150*10^9/L	29 (72.5)
IV	3 (7.5)	<150*10^9/L	11 (27.5)
Presence of other comorbidities		BRCA status	
Yes	38 (95)	BRCA1 mutation	2 (5)
No	2 (5)	BRCA2 mutation	3 (7.5)
ECOG score		BRCA wild-type	23 (57.5)
0	39 (97.5)	BRCA unknown	12 (30)
1	1 (2.5)	Histological type	
2	0	Serous	32 (80)
Surgical outcome		Endometrioid	4 (10)
R0	37 (92.5)	Other	4 (10)
R1	1 (2.5)	Prior use of bevacizumab	
No surgical	2 (5)	Yes	7 (17.5)
Type of surgery		No	33 (82.5)
NACT+IDS	21	Niraparib time was used	
Comprehensive staged surgery	17	<3 months	2 (5)
No surgical	2	≥ 3 months	38 (95)
Prior lines of chemotherapy		Platinum type at the time of frontline chemotherapy	
1	31 (77.5)	carboplatin	34 (85)
>1	9 (22.5)	cis-platinum/carboplatin+carboplatin	3 (7.5)
		Carboplatin+oxaliplatin	3 (7.5)

Table 2: TRAE.

TRAE	PBC	Niraparib	p value
	no. of patients (%)		
Any*	40 (100)	30 (75)	0.002
Grade ≥ 3*	28 (70)	16 (40)	0.012
Serious*	10 (25)	7 (17.5)	0.549
Any grade white blood cell count decreased	35 (87.5)	19 (47.5)	<0.001
Grade ≥ 3 white blood cell count decreased	12 (30)	5 (12.5)	0.065
Any grade red blood cell count decreased	37 (92.5)	23 (57.5)	<0.001
Grade ≥ 3 red blood cell count decreased	1 (2.5)	3 (7.5)	0.625
Any grade anemia	35 (87.5)	22 (55)	<0.001
Grade ≥ 3 anemia	18 (45)	8 (20)	0.041
Any grade platelet count decreased	16 (40)	12 (30)	0.424
Grade ≥ 3 platelet count decreased	6 (15)	5 (12.5)	1
Any grade neutrophil count decreased	34 (85)	14 (35)	<0.001
Grade ≥ 3 neutrophil counts decreased	23 (57.5)	7 (17.5)	<0.001

Table 3: Summary of adverse events.

Adverse event	niraparib maintenance therapy	
	Any grade	Grade ≥ 3
	number of patients (percent)	
Nausea	4(10%)	
Vomiting	4(10%)	
stomachache	2(5%)	
Dyspepsia	2(5%)	
Decreased appetite	1(2.5%)	
Fatigue or asthenia	5(12.5%)	
Abdominal distention	1(2.5%)	
Constipation	3(7.5%)	
Headache	1(2.5%)	
Insomnia	3(7.5%)	
Orbital pain	1(2.5%)	
A foreign body sensation in the chest	1(2.5%)	
Maculopapular rash	3(7.5%)	
Dark skin	1(2.5%)	
loss of weight	1(2.5%)	
Elevation of blood pressure	1(2.5%)	
white blood cell count decreased	19(47.5%)	5(12.5%)
red blood cell count decreased	23(57.5%)	3(7.5%)
Thrombocytopenia	12(30%)	5(12.5%)
Neutropenia	14(35%)	7(17.5%)
Anemia	22(55%)	8(20%)
Led to dose reduction	18(45%)	
Led to discontinuation of intervention	18(45%)	
Led to dose interruption	2(5%)	

of unrepaired DNA breaks leads to cell death [8,9]. This is known as "synthetic lethality". Niraparib is a highly selective inhibitor of PARP1/2 (a nuclear protein that detects DNA damage and promotes its repair) [10], and the most common adverse effect of niraparib is myelosuppression, with most interruptions of niraparib treatment due to myelosuppressive events [11].

The anti-tumor mechanism of PARP inhibitors (PARPi) overlaps with platinum-based drugs in DNA damage repair pathways. Patients who are effective to platinum-based chemotherapy are also more likely to be sensitive to PARPi. The dose-limiting toxicity of carboplatin is myelosuppression, and its non-hematologic adverse reactions are milder and fewer than those of cisplatin [12-14], and several studies have shown that the most common ≥ grade 3 adverse reactions of niraparib are also hematologic adverse reactions [15-17]. In this real-world study, we observed a lower rate of hematologic adverse effects with niraparib than with platinum-based chemotherapy in patients with advanced ovarian cancer. Niraparib maintenance therapy is better tolerated than platinum-based chemotherapy in this study. Due to the small sample size, larger sample size is needed for further verification.

In this study, all patients received a starting dose of niraparib of 200 mg/d according to their basal body weight and basal platelet count,

which was consistent with the Chinese prospective study [15,16]. The most common adverse reactions of any grade were hematologic adverse reactions, nausea, and fatigue, and there were 16 cases of ≥ grade 3 adverse reactions, all of which were hematologic adverse reactions, which were similar to the results of the NORA [15] study. A meta-analysis showed that niraparib adverse effects were significantly dose-related, and most of them could be controlled by suspending therapy, reducing dose, and treating symptomatic therapy [18]. In this study, during the maintenance treatment with niraparib, 16 patients experienced grade ≥ 3 adverse reactions, 18 patients reduced their dose due to adverse drug reactions, 18 patients discontinued their medication due to adverse drug reactions, 1 patient spontaneously terminated the drug due to stomach pain after taking the drug, and 1 patient terminated the drug due to recurrent ≥ grade 3 bone marrow suppression, which is consistent with the results of the meta-analysis [19] of the current clinical trial. In the context of the new crown epidemic, 8 patients stopped taking the drug for 1-4 weeks due to new coronavirus infection, and all patients passed the new coronavirus infection period safely.

In this study, we found that any grade of adverse blood reactions, including (decreased white blood cells, decreased red blood cells, anemia, and neutrophils), occurred during platinum-based chemotherapy and niraparib maintenance therapy in patients with ovarian cancer, and there was a correlation between grade ≥ grade 3 adverse reactions including (anemia, neutrophil decline). There was no statistically significant correlation between any grade of anemia and grade ≥ grade 3 leukocytopenia, grade ≥ grade 3 erythrocyte declines, and grade 3 thrombocytopenia ≥ the two periods. Due to the small sample size, it is not possible to obtain a valid correlation strength analysis, which requires more data for further validation. Based on this study, it is believed that the occurrence of serious hematologic adverse reactions with platinum-based chemotherapy may be a risk factor for patients to develop serious hematologic adverse reactions in maintenance therapy with niraparib. For patients with grade ≥ 3 anemias or neutropenia during chemotherapy, the choice of subsequent PARP inhibitor therapy may require more individualized consideration. More data are needed to clarify whether the timing of drug administration should be comprehensively selected according to the recovery of adverse reactions of previous chemotherapy and the results of review. Based on this study, we think that for patients who experienced ≥ grade 3 hematological adverse reactions during chemotherapy, the detection of blood indicators should be more stringent than that of patients who did not experience ≥ grade 3 hematological adverse reactions during chemotherapy.

Conclusion

In this real-world practice, we observed that patients with advanced ovarian cancer who experienced any grade and grade ≥ 3 TRAE during chemotherapy were well tolerated when treated with niraparib, particularly the incidence of any grade and grade ≥ 3 anemia, and neutrophil count decreased during niraparib treatment were significantly lower compared with that during chemotherapy.

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