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Research Article

Retrospective Evaluation of the Efficacy and Safety of Niraparib Maintenance; Real World Data on Turkish Early-Access Program

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Abstract

Objectives: The treatment of epithelial ovarian cancer has been revolutionized by the development of poly ADP-ribose polymerase (PARP) inhibitors which offer maintenance therapy options that extend progression-free survival (PFS).

Methods: Patients from sixteen institutions in Turkey who had International Federation of Gynecology and Obstetrics stage III or IV epithelial ovarian cancer and complete or partial response to at least four cycles of platinum-based chemotherapy were included in this retrospective study regardless of BRCA status and recurrence disease.

Results: A total of 67 patients were evaluated. The median age was 58. The median follow-up was 17.5 months. Median PFS was 8.3 months in BRCAwt and 10.9 months in BRCAmut group (p=0.033). There was no significant difference in mPFS between primary and recurrent patients (10.2 vs. 9.4 months, p=0.328). The most common grade 3/4 adverse events were anemia (32.8%), thrombocytopenia (16.4%), and neutropenia (16.4%).

Conclusion: The Turkish EAP's real-world data supports the efficacy and tolerability of niraparib in routine clinical practice and complements findings from randomized phase III trials.

Keywords: BRCA, maintenance, niraparib, ovarian cancer, toxicity

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The introduction of poly (ADP-ribose) polymerase (PARP) inhibitors significantly changed the treatment landscape for ovarian cancer. Several clinical trials have confirmed that PARP inhibitors were associated with significantly longer progression-free survival (PFS) compared to placebo in both platin sensitive primary and recurrent ovarian cancer.[1-5] The phase III PRIMA trial demonstrated the efficacy of niraparib for first-line maintenance therapy in newly diagnosed Breast Cancer mutant (BRCAmut) or HRD-positive metastatic ovarian cancer responsive to first-line platinum-based chemotherapy.[4] The phase III ENGOT-OV16/NOVA trial reported that niraparib maintenance after response to platinum-based chemotherapy significantly prolonged PFS compared to placebo in patients with platinum-sensitive recurrent ovarian cancer, regardless of the presence of BRCA mutations or HRD status.[3]

Niraparib was first approved with a recommended starting dose of 300 mg once daily. Further analysis of ENGOT-OV16/NOVA indicated that using a lower initial dose in patients under 77 kg or with a platelet count below 150 × 103/µl increased tolerability without reducing efficacy.[6] An individualized starting dosage (ISD) was confirmed in the randomized phase III PRIMA trial of maintenance niraparib following first-line chemotherapy and has been adopted as standard practice.[7] The NORA (with ISD in recurrent disease) and PRIME with ISD in newly diagnosed) trials showed that the ISD of niraparib significantly improved PFS compared to placebo, with a better safety profile than earlier trials utilizing a fixed starting dose.[8, 9]

Compared to randomized clinical trials, real-world studies are less restrictive, have broader inclusion criteria, and patients are more relevant to clinical practice. Until late 2023, niraparib was not covered by health insurance in Turkey. In 2022, an Early Access Program (EAP) was implemented for both primary and recurrent platinum-sensitive patients, regardless of BRCA status, and patients were able to receive maintenance treatment. The objective of this study was to assess both the efficacy and safety of niraparib in these patients and reveal the first PARP inhibitor maintenance experience in Turkey.

Methods

Study Design

This retrospective, non-interventional, multicenter real-world data aims to assess the safety and efficacy of niraparib in the treatment epithelial ovarian cancer patients within an EAP.

The primary endpoint of this retrospective study was PFS and overall survival (OS). Progression free survival was defined as the time from the initial niraparib dose to the initial progression event. Overall survival was defined as the initial of the niraparib to death. The secondary endpoint was treatment related adverse events identified by the treating physician.

Study Population and Treatment

Data from sixteen of the institutions participating in the Niraparib Turkish EAP was collected between June 2022 and June 2023. The inclusion criteria were as follows: (1) being older than 18 years of age at diagnosis; (2) had International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer, fallopian cancer, or primary peritoneal cancer that were histologically confirmed; (3) had germline pathogenic BRCA1 or BRCA2 mutant (BRCAmut) patients and BRCA wild (BRCAwt) patients; (4) had a complete or partial response to at least four cycles of platinum-based chemotherapy.

Patients who had platinum-resistant ovarian cancer (with a progression free interval of <6 months), started niraparib more than 16 weeks after their last platinum-based treatment, had a histological type other than high-grade serous or endometrioid cancer, FIGO stage I-II, hematological disease, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥3 were excluded.

Niraparib dose was administered according to ISD. For first-line maintenance treatment niraparib dose was based on body weight or platelet count (300 mg for patients weighing >77 kg with a platelet count >150,000/mL; 200 mg for patients weighing <77 kg and/or with a platelet count <150,000/mL). For recurrent disease niraparib dose was 300 mg.

Efficacy and Safety Assessments

Demographic data, clinicopathologic data, and surgical records of the included patients were obtained from their medical records. A computed tomography (CT) scan of the thorax and abdomen was conducted every 6–12 weeks in accordance with clinical practice at each institution to assess tumor response and progression in accordance with RECIST-v1.1.

The treating physicians evaluated the adverse events (AEs). Safety monitoring was conducted at baseline, at each subsequent evaluation visit, or as clinically indicated. Subsequent evaluation visits differed between centers (some evaluated once a week for the first month, some evaluated once every two weeks). Therefore, the evaluation was made based on the laboratory results of the 15th day after starting the drug. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment interruption and dose reduction dates were documented.

Statistical Analysis

No formal sample size calculation was conducted due to the exploratory nature of the study. The patient's clinical and demographic parameters were described using frequency and percentage for categorical variables and mean±standard deviation (SD) or median and interquartile range for continuous variables. The chi-square test (or Fisher's exact test) was employed to compare the groups in terms of categorical variables, whereas the Student t-test or Wilcoxon rank sum test was utilized for continuous variables, depending on the circumstances. The estimation of survival outcomes was conducted using the Kaplan-Meier method. The resulting Kaplan-Meier curves reflect the median survival time. The log-rank test was used to compare the survival curves between groups. A p-value <0.05 was considered statistically significant. The statistical analyses were conducted using SPSS version 27.

Results

Patient Population

A total of 67 patients were evaluated Thirty-six (53.7%) patients were BRCAmut, and 18 (26.9%) patients were BRCAwt. The median number of platinum-based chemotherapy cycles before niraparib maintenance was 6 (range 2 to 8).

The median time between chemotherapy and initiation of niraparib was 7 weeks (range 1 to 16). The median duration of niraparib treatment was 11.5 (range 1.00 to 18.25) months. The clinical and pathological characteristics of the patients are presented in Table 1.

Table 1. Clinical and pathological features of the patients

Age, years, median	58 (min: 33-max: 76)
BMI, (kg/m^2), median	27.3 (min: 17.6-max: 42.2)
ECOG PS	
0-1	57 (85.1%)
2	10 (14.9%)
FIGO stage	
3	51 (66.1%)
4	16 (23.9%)
Primary site	
Ovary	61 (91%)
Peritoneum	2 (3%)
Fallopian tube	4 (6%)
Disease status	
Primary	25 (37.3%)
Recurrence	42 (62.7%)
Previous bevacizumab treatment	
Yes	34 (50.7%)
No	33 (49.3%)
Neodjuvant chemotherapy	
Yes	22 (32.8%)
No	45 (67.2%)
Debulking surgery	
Primary debulking surgery	30 (44.7%)
Interval debulking surgery	21 (31.4%)
No surgery	16 (23.9%)
BRCA status	
BRCA-1	23 (34.3%)
BRCA-2	13 (19.4%)
BRCA-wild	18 (26.9%)
Unknown	13 (19.4%)
Response to platinum-based chemotherpy	
Partial response	31 (46.3%)
Complete response	36 (53.7%)
CA-125 level before niraparib initiation, median	16 (3.2-190)
Starting dose	
200 mg	25 (37.3%)
300 mg	42 (62.7%)
Weight	
<77 kg	43 (64.2%)
≥77 kg	24 (35.8%)
Type of healthcare center	
Secondary	4 (6%)
Tertiary	47 (70.1%)
Private	16 (23.9%)

BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Efficacy

The median follow-up time was 17.5 (range 4.75 to 20.75) months. The median PFS was 8.3 (95%CI: 6.8-9.8) months in BRCAwt and 10.9 (95%CI: 9.9-11.8) months in BRCAmut group (p=0.033 via the log-rank test). There was no significant difference in mPFS between primary and recurrent patients (10.2 vs. 9.4 months, p=0.328 via the log-rank test). Median PFS of the patients according to BRCA status is shown in Figure 1.

Radiological response data were available for 55 of the 67 patients with measurable disease. Partial response was reported in 22 patients (32.8%), 10 (14.9%) had stable disease as the best response, 23 (34.3%) had disease progression. Among of the 23 progression events, 14 (60.9%) occurred in the BRCA wild group, while 9 (39.1%) occurred in the BRCAmut group.

There was a total of 12 (18.9%) deaths, with 2 (5.4%) events in the BRCAmut group and 10 (33.3%) events in the BRCAwt group. Since the median OS could not be reached, the 12-month OS rate was analyzed. In the whole population, the 12-month OS rate was 74.6% (95% CI 68.2-79.6%).

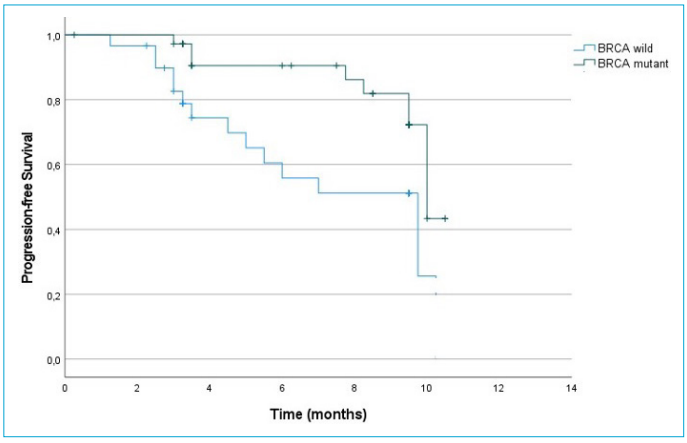

Figure 1. Median progression free survival of the patients according to BRCA status.

The 12-month OS rate was 70% (95% CI 68.2.0-73.6%). in the BRCAwt group and 78.4% (95% CI 72.0-79.6%) in the BRCAmut group.

The subsequent treatment regimens for the 23 patients (34.3%) who experienced disease progression with niraparib were as follows: Out of the patients, 12 (17.9%) were administered liposomal doxorubicin-bevacizumab, 9 (13.4%) received platinum-gemcitabine-bevacizumab, 1 (1.5%) received pemetrexed, and 1 (1.5%) received cyclophosphamide for a minimum of 2 cycles.

Safety

Grade 1 and 2 AEs were reported in 38 (56.7%) patients. The rate of AEs in grade 3 and 4 was 55.2%. The most common grade 3/4 AEs were anemia (32.8%), thrombocytopenia (16.4%), and neutropenia (16.4%). The most of all grade AEs (68%, 72%, 56% of all grade anemia, thrombocytopenia, and neutropenia, respectively) occurred in the first 3 months. In 33 patients, niraparib treatment was interrupted because of AEs. The median duration of treatment interruption was 14 (7–30) days. Seven (10.4%) patients had discontinued niraparib. Four of them had grade 4 thrombocytopenia; one had acute renal failure, one had acute myeloid leukemia; and one had pure red cell aplasia. The number of patients who underwent dose reduction was 29 (43.3%).

During the initial three months of treatment, statistically significant reductions in hemoglobin (11.8±1.3 vs. 9.1±2.1 gr/Dl, p<0.001 via paired t test), platelets (258±87 vs. 141±92 x103/uL, p<0.001 via paired t test), neutrophils (3.6±2.2 vs. 1.9±1.0 x103/uL, p<0.001 via paired t test) were observed when compared to the pre-treatment period. Additionally, creatinine levels increased significantly during the first three months of treatment (0.70±0.21 vs.1.03±0.34 mg/dL, p<0.001 via paired t test). Laboratory changes before and after the treatment and frequency of AEs are shown in Tables 2 and 3.

Table 2. Laboratory parameters before and after the treatment.

	Before	After	p*
Hemoglobin (g/dL)	11.8±1.3	9.1±2.1	<0.001
Platelet (x10.e3/uL)	258±87	141±92	<0.001
Neutrophil (x10.e3/uL)	3.6±2.2	1.9±1.0	<0.001
WBC (x10.e3/uL)	6.1±2.4	4.0±2.1	<0.001
Creatinine (mg/dL)	0.70±0.21	1.03±0.34	<0.001

*Paired t test. The values are means±standart deviations; WBC: white blood cells.

Table 3. Hematological and non-hematological adverse events.

	All grades	Grade ≥3	Treatment interruption	Treatment discontinuation
Anemia	42 (62.7%)	22 (32.8%)	9 (13.4%)	0
Thrombocytopenia	28 (41.8%)	11 (16.4%)	13 (19.4%)	4 (6.0%)
Neutropenia	44 (65.7%)	11 (16.4%)	5 (7.5%)	0
Nausea	23 (34.3%)	5 (7.5%)	2 (3%)	0
Constipation	9 (13.5%)	0	0	0
Diarrhea	4 (6.0%)	1 (1.5%)	0	0
Hypertension	14 (20.9%)	0	1 (1.5%)	0
Tachycardia	5 (7.5%)	1 (1.5%)	0	0
Decreased appetite	4 (6.0%)	0	0	0
Arthralgia	5 (7.5%)	0	0	0
Creatinine increase	8 (12%)	2 (3%)	1 (1.5%)	1 (1.5%)
AML	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)
Pure red cell aplasia	1 (1.5%)	1(1.5%)	1 (1.5%)	1 (1.5%)

AML: Acute myeloid leukemia.

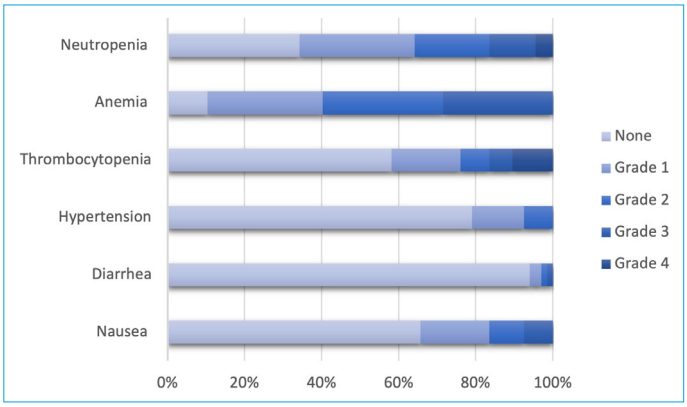

Figure 2. Treatment-related adverse events (TRAEs) rates according to CTCAE version 5.0.

Discussion

In this study, 67 ovarian cancer patients who received niraparib within the scope of anEAP in Turkey were evaluated, and 9.8 months of mPFS was found in the whole group. As reported in pivotal trials, niraparib contributed to PFS in platinum-sensitive ovarian cancer in both first-line and recurrent platinum-sensitive patients.[3, 7] In the NOVA study, mPFS was 9.3 months in the BRCAwt recurrent ovarian cancer cohort.[3] In our study, mPFS was 8.3 months in the BRCAwt group, and it was consistent with pivotal trials. In addition, in other real-life data where BRCAwt recurrent patients were retrospectively evaluated, mPFS was 9.1, 6.9 and 8.6 months, and our BRCAwt cohort PFS result was also consistent with them.[10-12]

On the other hand, in our study, the mPFS (10.9 months) in the BRCAmut cohort was not consistent with our expectations and the literature. In the PRIMA and NOVA trials, mPFS was 21.9 and 21.0 months in BRCAmut primary and recurrent ovarian cancer patients, respectively.[3, 7] This might be related to our higher rate of treatment interruption (49.2%) and treatment discontinuation (10.4%). It might also be due to the small size and heterogeneity of our patient population.

Niraparib toxicities had been well demonstrated in several phase III trials and their update analyses.[6, 8, 13, 14] Data from these trials demonstrated that the most common grade 3-4 AEs of niraparib were nausea, vomiting, and hematological toxicities. These are dose-limiting toxicities and lead to dose reductions and treatment interruptions. However, patients in clinical trials may not be representative of the typical patient population, limiting generalization. In real-life data reported to date, hematological toxicities have been reported at a higher rate than in pivotal trials. In a retrospective study reported in Spain with 316 patients with recurrent ovarian cancer, the rates of grade≥3 thrombocytopenia, anemia, and neutropenia were 21%, 15%, and 6%, respectively.[10] These rates were 13%, 16%, and 7% in another real-life data where 94 recurrent ovarian cancer patients were evaluated.[11] In our study, the rates were 16.4%, 32.8%, and 16.4%, and when compared to other retrospective data, the rates of grade ≥3 thrombocytopenia were similar; however, the rates of anemia and neutropenia were higher. A factor that predicts increased hematological toxicity has not been identified to date, so we can explain the increased toxicity with the lower rate of ISD in our study. Another reason for the higher AE rates might be the lack of close toxicity follow-up. Early detection of hematological toxicity with close hemogram monitoring, particularly in the initial months of treatment, allows for early dose adjustments, which play an important role in the management of niraparib AEs in clinical practice. In NORA trial, the median time for the development of severe hematologic AEs such as thrombocytopenia, anemia, and neutropenia were 23, 85, and 29 days, respectively and with effective management these AEs resolved in 10, 8, and 13 days.[9]

In the PRIMA study, grade ≥3 thrombocytopenia, anemia, and neutropenia was 33.1%, 23.7%, 29.5% and these rates were higher compared with the PRIME trial (14.1%, 18%, and 17.3%).[4,15] This was because ISD was applied to only 35% of patients in the PRIMA trial and all the patients in the PRIME trial.[8] The retrospective RADAR analysis of the NOVA trial revealed that patients having a baseline bodyweight <77 kg or platelet <150 × 103/μl were administered an average lower dose of niraparib, 207 mg per day.[16] Importantly, this reduction in dose did not have any negative impact on the efficacy of the treatment. After that, the protocol of the phase III PRIMA trial was modified to include an ISD of niraparib.[4]

Hematologic toxicity remains the main dose limiting toxicity of PARPi treatment. There are currently no approaches to predicting patients at higher risk. Therefore, regular complete blood count monitoring is recommended.[17-19] We explored the significant decrease in hematological parameters after niraparib and mentioned the importance of close hemogram monitoring. Additionally, in our study, more than half of the patients required a dose reduction. Dose adjustments in other real-world studies occurred in 14 to 44% of patients.[10, 11, 20] The lower rate of ISD in our study may have also contributed to these higher rates of dose modifications.

There are several limitations in our study. The first of these is the small number of patients. According to the information we received through EAP coordinator, patients were included from approximately 25 centers. We accessed and included sixteen of them. We estimate that we were unable to reach approximately 20 patients in the centers we could

not access. Secondly, the study population was heterogeneous with primary and recurrent diseases. Another limitation is that somatic BRCA alterations and HRD status could not be examined due to their high cost. This has the potential to alter the distribution of patients according to their BRCA status. Despite these limitations, our study has several strengths. This is the first study to evaluate the efficacy and safety of niraparib in Turkish ovarian cancer patients in a real-world setting, providing valuable insights into its efficacy and reliability outside the confines of a clinical trial. Our study also underscores the importance of close monitoring and early intervention in managing AEs, contributing to the growing body of evidence supporting the safety management of niraparib in clinical settings.

Conclusion

The Turkish EAP supports the efficacy and tolerability of niraparib in routine clinical practice and complements findings from randomized phase III trials. Future research should focus on improving dose reduction strategies, exploring combination therapies, and developing more personalized approaches to more closely monitor and manage AEs. These efforts are important to maximize the clinical benefits of niraparib while minimizing its AEs and thereby improving the quality of life of ovarian cancer patients.

Disclosures

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the institutional ethics committee (date: Nov 21, 2022, no: 4230081c-e762-44a3-96f6-7974d89337b3) and conducted in accordance with the related privacy statements and applicable regulatory requirements.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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