Safety and management of niraparib monotherapy in ovarian cancer clinical trials

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ABSTRACT

Niraparib is a poly (ADP-ribose) polymerase inhibitor that has shown a significant improvement in progression-free survival irrespective of biomarker status in patients with advanced epithelial ovarian cancer. This review focuses on the adverse events associated with niraparib and their management to maintain efficacy of niraparib treatment and improve quality of life for patients. In five trials assessing efficacy of niraparib in patients with advanced epithelial ovarian cancer (PRIMA, NOVA, NORA, QUADRA, and PRIME), treatment-emergent adverse events of any grade were reported in nearly all patients (≥99%) receiving niraparib; the events were grade ≥3 in 51–74% of patients. Across all lines of therapy, treatment-emergent adverse events led to dose interruptions in 62–80% of patients receiving niraparib and dose reductions in 47–71%. Hematologic events were most frequently reported, including thrombocytopenia, anemia, and neutropenia. Common non-hematologic events included gastrointestinal events, which were generally low grade (<5% were grade ≥3). Clinical strategies to manage these and other events, such as fatigue and insomnia, cognitive behavioral therapy and pharmacologic agents, are summarized. Once-daily niraparib dosing may be advantageous for some patients for many reasons, including night-time dosing which may help alleviate gastrointestinal symptoms. An individualized starting dose (determined by baseline body weight and platelet count) of niraparib demonstrated an improved safety profile while maintaining efficacy. Patients receiving the niraparib individualized starting dose had fewer grade ≥3 adverse events, dose interruptions, and dose reductions than patients receiving a fixed starting dose. The safety profile of niraparib across five pivotal studies in advanced epithelial ovarian cancer was consistent across multiple lines of treatment, including as maintenance therapy in first-line and recurrent settings and as treatment in heavily pre-treated patients. Long-term safety data from the NOVA trial confirmed that, with appropriate and early dose modifications, niraparib is well tolerated.

INTRODUCTION

Standard treatment for newly diagnosed epithelial ovarian cancer is cytoreductive surgery and platinum-based chemotherapy. Despite an initial positive response, 70–80% of patients will experience disease recurrence within 2 years of completing first-line therapy.[1] The introduction of inhibitors of poly (ADP-ribose) polymerase (PARP), a key regulator of DNA damage repair, has significantly enhanced treatment options for advanced epithelial ovarian cancer.[1 2] Niraparib is a PARP inhibitor that improved progression-free survival as a maintenance therapy in multiple clinical trials with manageable toxicity,[3–6] leading to approval for clinical use.[7 8]

Niraparib was first approved by the Food and Drug Administration (FDA)[7] and the European Medicines Agency (EMA)[8] in 2017 as maintenance treatment of recurrent epithelial ovarian cancer after complete response/partial response to platinum-based chemotherapy. Approval was extended in 2019 (FDA) to treatment in the fourth (or greater) line of homologous recombination deficient epithelial ovarian cancer (defined by either a deleterious or suspected deleterious breast cancer gene (*BRCA*) mutation or genomic instability) in patients whose tumor(s) had progressed >6 months after response to the last platinum-based chemotherapy. However, this indication was voluntarily withdrawn in the USA in September 2022 based on the potential detrimental effect observed with other PARP inhibitors on overall survival in late-line treatment settings. In 2020, niraparib was approved (FDA/EMA) as first-line maintenance therapy in patients with advanced epithelial ovarian cancer (European indication specifies International Federation of Gynecology and Obstetrics (FIGO) stage 3 and 4)[8] and who had complete response/partial response to platinum-based chemotherapy.[9–11] The FDA approval of niraparib as second-line maintenance therapy was recently amended to include only patients with deleterious or suspected deleterious *BRCA* mutation.[12]

Niraparib treatment significantly improved progression-free survival irrespective of biomarker status in patients with advanced epithelial ovarian cancer who responded to platinum-based chemotherapy.[9–11] Despite improvements in progression-free survival, patients may experience adverse events with niraparib treatment. This review article focuses on adverse events associated with quality of life (QoL) for patients receiving niraparib.

PARP INHIBITOR-RELATED ADVERSE EVENTS

Many adverse events reported with the use of niraparib in patients with epithelial ovarian cancer in clinical trials occur across PARP inhibitors as a drug class[13] and are associated with on- and off-target

effects.[14] Hematologic adverse events are most commonly reported, and are a known class-effect adverse event due to trapping of PARP1 by PARP inhibitors.[14] Gastrointestinal adverse events also occur frequently with PARP inhibitor therapy.[13–15] Approximately 10–25% of patients receiving PARP inhibitor maintenance therapy also experience neurological adverse events including insomnia or headache; however, these events are generally low grade.[14]

Some PARP inhibitor-related adverse events are more frequently reported with particular agents[16]—for example, hypertension and tachycardia with niraparib[17–19] and transient liver enzyme elevations with rucaparib.[14 17–20] Cardiovascular adverse events such as hypertension are likely explained by niraparib's off-target effects of pharmacologic inhibition of dopamine, norepinephrine, and serotonin transporters.[14] As each PARP inhibitor has different binding affinities for PARP1, PARP2, and PARP3, the on-target effects of PARP inhibition can vary between drugs of this class.[19] Differences in the systemic effects of these drugs also likely contribute to variations in their safety profiles. For example, niraparib is metabolized primarily by carboxylesterases into an inactive metabolite which subsequently undergoes glucuronidation, whereas olaparib and rucaparib are primarily metabolized via hepatic oxidative metabolism.[21] All are eliminated predominantly through the hepatobiliary and renal routes.[21–24] Additionally, niraparib does not appear to have induction or inhibitory effects on cytochrome P450 enzymes,[7] and has no contraindication listed in the prescribing information for concomitant use with other cytochrome P450 enzyme inducers or inhibitors. Unlike other PARP inhibitors, niraparib does not need dose modifications in this context.[21] This difference in metabolism to rucaparib and olaparib may explain the potential effects on liver enzyme levels. Elevations in creatinine have been described in 11–15% of patients treated with rucaparib and olaparib due to on-target effects on renal transporters which secrete creatinine; however, these are not usually associated with renal injury.[19] Notably, niraparib was not associated with elevated serum creatinine.[19]

Aggregation of the adverse event data from clinical trials is valuable to the healthcare professional in routine clinical practice.

NIRAPARIB CLINICAL TRIALS AND SAFETY SUMMARY

The clinical development program for niraparib in advanced epithelial ovarian cancer includes five pivotal studies: the PRIMA/ENGOT OV26/GOG 3012 (NCT02655016)[3] and PRIME (NCT03709316)[6] studies of niraparib as first-line maintenance treatment in platinum-responsive patients[3]; the NOVA/ENGOT OV16 (NCT01847274)[4] and NORA (NCT03705156)[5] studies of niraparib as maintenance treatment in platinum-sensitive recurrent disease; and the QUADRA study (US only; NCT02354586)[3] of niraparib treatment in patients with later-line epithelial ovarian cancer (see Online Supplemental Table 1).

The safety profile of niraparib in the PRIMA, PRIME, NOVA, NORA, and QUADRA trials was consistent across multiple lines of treatment (Table 1).[3–6] Treatment-emergent adverse events of any grade occurred in nearly all patients (≥99%) receiving niraparib, with events grade ≥3 in 51–74% of patients. Serious treatment-emergent adverse events occurred in 18–43% of patients across studies, and fatal treatment-emergent adverse events occured in ≤1% of patients overall (Table 1). Across all lines of therapy, treatment-emergent adverse events led to dose interruptions and reductions in 62–80% and 40–71% of patients, respectively. Treatment-emergent adverse events led to discontinuation in 7–12% of patients in the first-line maintenance setting, 4–15% of patients as recurrent maintenance therapy, and 21% of patients as late-line treatment (Table 1).

The PRIMA trial prospectively assessed the use of an individualized starting dose of niraparib in some patients. The trial protocol

Table 1 Summary of treatment-emergent adverse event outcomes from the PRIMA, NOVA, NORA, and QUADRA trials of niraparib in epithelial ovarian cancer

Treatment-emergent adverse events, n (%)	PRIMA fixed starting dose[27] (n=315)	PRIMA individualized starting dose[27] (n=169)	PRIME[6] individualized starting dose (n=255)	NOVA[4] (n=367)	NORA[5] individualized starting dose* (n=177)	QUADRA[3] (n=463)
Any grade	313 (99.4)	165 (97.6)	253 (99.2)	367 (100)	177 (100)	461 (99.6)
Treatment related	306 (97.1)	160 (94.7)	249 (97.6)	358 (97.5)	176 (99.4)	443 (95.7)
Grade ≥3	239 (75.9)	102 (60.4)	139 (54.5)	272 (74.1)	90 (50.8)	338 (73.0)
Treatment related	228 (72.4)	88 (52.1)	125 (49.0)	237 (64.6)	79 (44.6)	266 (57.5)
Serious	111 (35.2)	45 (26.6)	48 (18.8)	110 (30.0)	31 (17.5)	197 (42.5)
Treatment related	83 (26.3)	35 (20.7)	38 (14.9)	62 (16.9)	23 (13.0)	91 (19.7)
Leading to						
Dose interruption	264 (83.8)	121 (71.6)	160 (62.7)	253 (68.9)	Not reported	288 (62.2)
Dose reduction	239 (75.9)	104 (61.5)	103 (40.4)†	244 (66.5)	106 (59.9)	218 (47.1)
Discontinuation	35 (11.1)	23 (13.6)	17 (6.7)	54 (14.7)	7 (4.0)	98 (21.2)
Death‡	2 (0.6)	0 (0)	1 (0.4)	0 (0)	0 (0)	9 (1.9)

All adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
*94% of patients randomized to niraparib in NORA received an individualized starting dose.
†In PRIME, dose reduction includes both direct dose reduction and dose reduction following treatment interruption.
‡In PRIMA, no deaths were treatment related. In QUADRA, 1 death due to gastric hemorrhage was considered treatment related. In PRIME, 1 death due to acute myeloid leukemia was considered treatment related. There were no on-treatment deaths reported during the NOVA and NORA studies.

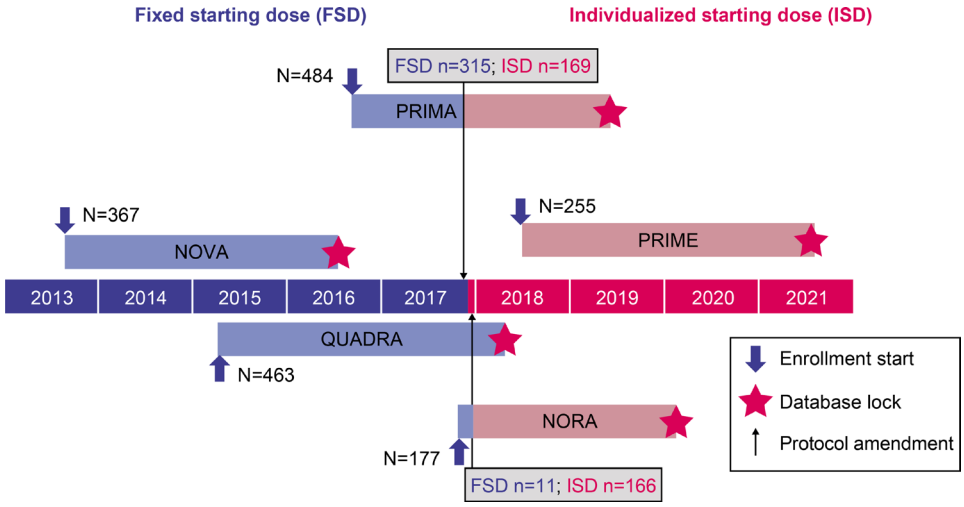

Figure 1 Timeline for primary analyses of pivotal studies of niraparib highlighting dosing regimens.

began with all patients receiving a fixed starting dose of niraparib 300 mg once daily, but was amended after 65% enrollment was achieved (in November 2017) to allow an individualized starting dose of niraparib (200 mg once daily for patients with body weight <77 kg or baseline platelet count <150 000/µL; 300 mg once daily if body weight ≥77 kg and baseline platelet count ≥150 000/µL; Figure 1).[3] This regimen was determined in a retrospective analysis of the NOVA study[25] and was also incorporated in the NORA study, but from an earlier point (after only 11/177 (6%) patients randomized to niraparib received a fixed starting dose).[5] The PRIME study used an individualized starting dose from trial initiation.[6] The QUADRA study used a fixed starting dose throughout.[26] Patients receiving the niraparib individualized starting dose in PRIMA had fewer grade ≥3 adverse events as well as fewer dose interruptions and dose reductions than patients receiving a niraparib fixed starting dose[27]; however, efficacy was maintained (hazard ratios for risk of progression or death with niraparib compared with placebo were 0.69 (95% CI 0.48 to 0.98) for individualized starting dose vs 0.59 (95% CI 0.46 to 0.76) for fixed starting dose). Rates of grade ≥3 and serious adverse events were also comparatively low in NORA, in which most patients randomized to niraparib received an individualized starting dose, as well as in PRIME, in which all patients received an individualized starting dose (Table 1). A post hoc analysis of QUADRA also reinforced the value of baseline platelet count and body weight and observed similar findings.[26]

In PRIMA, post hoc assessment of the niraparib safety profile in patients with *BRCA* wild-type or *BRCA* mutated ovarian cancer showed a similar incidence of any grade, grade ≥3, and serious treatment-emergent adverse events compared with the overall study population, and comparable trends for treatment-emergent adverse events leading to dose interruption, dose reduction, and treatment discontinuation (see Online Supplemental Table 2).[28 29] Within both *BRCA* wild-type and *BRCA* mutated sub-groups, patients receiving an individualized starting dose had an improved safety profile compared with patients receiving a fixed starting dose. Overall efficacy and QoL were maintained in each sub-group.[28 29]

In PRIMA, there were no remarkable differences in adverse event profiles in post hoc analyses by age (<65 vs ≥65 and <75 vs ≥75 years).[30] In NOVA, the frequency and severity of adverse events were similar in patients <70 and ≥70 years of age.[31] Long-term safety data from the NOVA trial confirmed that niraparib is well tolerated with appropriate dose modifications.[32 33] Adverse events leading to dose reductions were highest in the first month and continued to decline up to month 48; dose interruptions followed a similar trend. Discontinuations due to the most common hematological treatment-emergent adverse events such as thrombocytopenia, anemia, and neutropenia were low, remaining <5% across all time intervals.[32] A similar analysis of the NORA trial showed that the majority of treatment-emergent adverse events occurred primarily in the first month of niraparib treatment and decreased substantially thereafter with dose modifications.[34]

NIRAPARIB ADVERSE EVENTS: CLINICAL TRIAL DATA, GRADING, MONITORING, AND MANAGEMENT

Hematologic Adverse Events

Niraparib Trial Data

The most common treatment-emergent adverse events associated with niraparib in PRIMA, PRIME, NOVA, NORA, and QUADRA were hematologic, including thrombocytopenia, anemia, neutropenia, and leukopenia (see Online Supplemental Table 3). Grade ≥3 thrombocytopenia/decreased platelet count, anemia, and neutropenia/decreased neutrophil count were reported in >10% (and up to 34%) of patients across the study populations (see Online Supplemental Table 3).[3–6] Hematologic treatment-emergent adverse events tend to occur during the first 3 months of niraparib treatment (see Online Supplemental Figure 1) and are not cumulative if managed with appropriate dose modifications (see Management section).[13 32 33] In NOVA, overall hematologic treatment-emergent adverse events (anemia, neutropenia, and thrombocytopenia) occurred primarily in the first year of niraparib treatment (incidence from month 1 to month 6 was 28% vs 8%, respectively, for anemia and 14% vs 1% for neutropenia) and decreased thereafter.[33] The median time to onset of grade ≥3 hematologic treatment-emergent adverse events thrombocytopenia, anemia, and neutropenia was 23, 85, and 29 days, respectively and, with appropriate management strategies, had a time to resolution of 10, 8, and 13 days. Thrombocytopenia, anemia, and neutropenia events led to dose reductions in 40%, 19%, and 9% of patients, respectively, and dose interruptions in 38%,

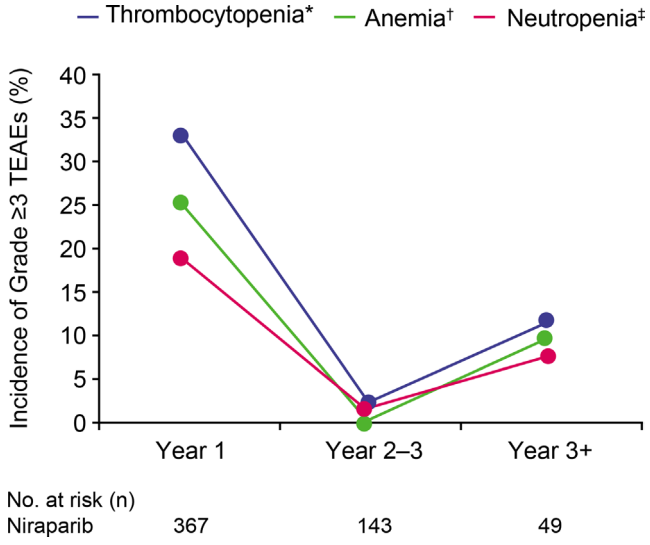

Figure 2 Incidence of grade ≥3 hematologic treatment-emergent adverse events (TEAEs) over time in NOVA safety population. *Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. †Anemia includes reports of anemia and decreased hemoglobin count. ‡Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

20%, and 15% during the NOVA study; discontinuations ranged between 1% and 3% of patients. Overall, the incidence of grade ≥3 hematologic treatment-emergent adverse events decreased after the first year of niraparib treatment and thereafter (Figure 2).[33]

Any-grade hematologic and grade ≥3 adverse events were less frequent when patients received an individualized starting dose rather than a fixed starting dose in PRIMA (see Online Supplemental Table 3).[27] Grade ≥3 thrombocytopenia decreased from 48% with a fixed starting dose to 21% with an individualized starting dose. Grade ≥3 anemia and neutropenia events decreased from 36% and 24% with a fixed starting dose to 22% and 15%, respectively, in patients receiving an individualized starting dose. In the NORA study, in which 96% of patients randomized to niraparib received an individualized starting dose, rates of grade ≥3 hematologic adverse events were generally lower than reported in PRIMA, NOVA, or QUADRA (anemia 15%, thrombocytopenia 11%, neutropenia 20%; Online Supplemental Table 3).[5] This trend was mirrored in the PRIME study in which all patients received an individualized starting dose of niraparib, with similarly low rates of grade ≥3 hematologic adverse events (18%, 14%, and 17%, respectively; Online Supplemental Table 3).[6] These results suggest that an individualized starting dose is useful for mitigating the potential effects of niraparib treatment on blood counts.[5 6]

Hematologic adverse events may be of particular concern in older patients with cancer because of a decline in hematopoietic reserves.[31] In PRIMA, any-grade and grade ≥3 hematologic treatment-emergent adverse events were generally similar in patients aged <65 and ≥65 years and in patients aged <75 and ≥75 years, with slight increases in any-grade and grade ≥3 thrombocytopenia in patients aged ≥65 and ≥75 years (Table 2).[35] A decrease in grade ≥3 thrombocytopenia events was observed in patients receiving an individualized starting dose compared with those receiving a fixed starting dose for all age groups. In NOVA, the incidence of overall myelosuppression events showed no age-related difference in patients <70 and ≥70 years of age (76% and 79%, respectively). The most common grade ≥3 adverse events in patients aged ≥70 years receiving niraparib were thrombocytopenia (34%), neutropenia (16%), and anemia (13%).[31]

Myelodysplastic syndrome and acute myeloid leukemia are rare hematologic events associated with PARP inhibitor therapy,[14] with an incidence of <1.5% in initial reports for patients receiving niraparib in the PRIMA (0.2%), PRIME (0.8%), NOVA (1.4%), and QUADRA trials (0.2%).[3 4 6 13] One unclassified fatal case of treatment-related acute leukemia was reported in a patient treated with niraparib after the primary cut-off date in the NORA study.[5 6] With longer-term follow-up and administration of subsequent therapies in the NOVA study, 3.5% (13/367) of patients receiving niraparib developed myelodysplastic syndrome/acute myeloid leukemia compared with 1.7% (3/179) receiving placebo . Additionally, there was a higher risk of myelodysplastic syndrome/acute myeloid leukemia in germline *BRCA* mutated vs non-germline *BRCA* mutated sub-groups for patients receiving niraparib (69% (9/13) vs 31% (4/13)).[33]

Grading, Monitoring, and Management

Grading of anemia, decreased platelet count, and decreased neutrophil count is summarized in Table 3.[36] There are several recommendations for the monitoring and management of hematologic adverse events (Table 3).[20 37] These include recommendations regarding treatment initiation, adverse event monitoring, and patient management. With regard to treatment initiation, the niraparib label recommends that treatment should not be started until patients have recovered from hematologic toxicity caused by previous chemotherapy (to grade ≤1). In the maintenance setting,

Table 2 Hematologic adverse events of niraparib treatment in older patients in the PRIMA and NOVA trials

	PRIMA individualized starting dose				PRIMA fixed starting dose				NOVA	
Grade ≥3 adverse events, n (%)	<65 y (n=100)	≥65 y (n=69)	<75 y (n=152)	≥75 y (n=17)	<65 y (n=194)	≥65 y (n=121)	<75 y (n=278)	≥75 y (n=37)	<70 y (n=306)	≥70 y (n=61)
Thrombocytopenia*	18 (18.0)	18 (26.1)	30 (19.7)	6 (35.3)	83 (42.8)	69 (57.0)	129 (46.4)	23 (62.2)	103 (33.7)	21 (34.4)
Anemia†	29 (29.0)	9 (13.0)	34 (22.4)	4 (23.5)	69 (35.6)	43 (35.5)	103 (37.1)	9 (24.3)	85 (27.8)	8 (13.1)
Leukopenia‡	18 (18.0)	9 (13.0)	26 (17.1)	<1 (1.3)	45 (23.2)	33 (27.3)	67 (24.1)	11 (29.7)	67 (21.9)	12 (19.7)

*Thrombocytopenia event includes thrombocytopenia and platelet count decrease.
†Anemia event includes anemia and hemoglobin decrease.
‡Leukopenia event includes leukopenia, white blood cell count decrease, lymphocyte count decrease, lymphopenia, monocyte count decrease, and neutropenia event.
y, years.

Table 3 Hematological adverse events grading and management

Hematologic*: obtain complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter for clinically significant changes		
Adverse event	**Grade**	**Management**
Anemia	Grade 1 Hgb <LLN–10.0 g/dL; <LLN–6.2 mmol/L; <LLN–100 g/L Grade 2 Hgb <10.0–8.0 g/dL; <6.2–4.9 mmol/L; <100–80 g/L Grade 3 Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated Grade 4 Life-threatening consequences; urgent intervention indicated	If hemoglobin <8 g/dL: ► Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until hemoglobin returns to ≥9 g/dL ► Resume niraparib at a reduced dose per label-recommended dose modifications† for hematologic toxicity[20 37] ► Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily
Platelet count	Grade 1 <LLN–75 000/mm^3; <LLN–75.0x10^9/L Grade 2 <75 000–50 000/mm^3; <75.0–50.0x10^9/L Grade 3 <50 000–25 000/mm^3; <50.0–25.0x10^9/L Grade 4 <LLN–75 000/mm^3; <LLN–75.0x10^9/L	If platelet count is <100 000/µL: First occurrence: ► Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL ► Resume niraparib at same or reduced dose per label-recommended dose modifications† for hematologic toxicity[20 37] ► If platelet count is <75 000/µL, resume at a reduced dose Second occurrence: ► Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL ► Resume niraparib at a reduced dose per label-recommended dose modifications ► Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily
Neutrophil count	Grade 1 <LLN–1500/mm3;<LLN–1.5x109/L Grade 2 <1500–1000/mm3 ; <1.5–1.0x109 /L Grade 3 <1000–500/mm3 ; <1.0–0.5x109 /L Grade 4 <500/mm3 ; <0.5×109 /L	If neutrophil count is <1000/µL: ► Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1500/µL ► Resume niraparib per label-recommended dose modifications† for hematologic toxicity ► Discontinue niraparib if neutrophils have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100mg once daily*

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue niraparib.
†For 200 mg starting dose: first dose reduction is to 100 mg/day (one 100 mg capsule); if a second dose reduction is needed, discontinue treatment. For 300 mg starting dose: first dose reduction is to 200 mg/day (two 100 mg capsules), second dose reduction is to 100 mg/day (one 100 mg capsule); if dose reductions <100 mg/day are required, discontinue treatment.
Hgb, hemoglobin; LLN, lower limit of normal.

niraparib treatment should commence no later than 12 weeks after the last platinum-containing regimen and no later than 8 weeks after for recurrent epithelial ovarian cancer. To monitor hematological toxicities, blood counts should be taken weekly for the first month, monthly for the next 11 months, and then periodically thereafter and mitigated with dose modifications where necessary (Table 3). Patients should be advised to contact their healthcare provider if they experience any of the following symptoms: weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, and blood in urine or stool. In addition, laboratory findings of low blood cell counts or a need for blood transfusions,may be suggestive of hematologic toxicity or myelodysplastic syndrome/acute myeloid leukemia. Hematology referral should be considered for patients with persistent cytopenia (ie, toxicity does not recover within 4 weeks) or abnormal complete blood count findings for bone marrow biopsy/aspirate, and blood sample for cytogenetics to rule out myelodysplastic syndrome/acute myeloid leukemia.[14] If myelodysplastic syndrome/acute myeloid leukemia is confirmed, niraparib treatment should be discontinued.

Non-Hematologic Adverse Events

Gastrointestinal Adverse Events

Niraparib Trial Data

In the pivotal trials of niraparib in advanced epithelial ovarian cancer, gastrointestinal events frequently occurred but were generally low grade. The incidence of grade ≥3 events was <5% across niraparib trials, except the QUADRA trial of patients with later-line epithelial ovarian cancer where the incidence was <10% (see Online supplemental table 3).[3–6] Across the epithelial ovarian cancer trials, the most frequently reported any-grade treatment-emergent adverse events with niraparib were nausea, vomiting, and constipation, occurring in 45–74%, 20–45%, and 21–40% of patients, respectively (Online supplemental table 3); diarrhea (any grade) was

reported in 9–19% of patients.[3–6] In the NOVA trial, these events tended to occur early and decreased over the first 3 months. The incidence of nausea and vomiting greatly reduced between the first and second month with niraparib (62% vs 13%, respectively, and 20% vs 6%).[32] Treatment modifications including dose reductions and interruptions occurred in <10% of patients in NOVA.[4 32 38] Additional frequent low-grade gastrointestinal adverse events reported with niraparib and other PARP inhibitors included abdominal pain or distension, decrease in appetite, and dyspepsia.[14] Abdominal pain was often reported in the placebo arms of PARP inhibitor clinical trials, likely related to underlying disease and progression.[14]

Grading, Monitoring, and Management

Grading of common gastrointestinal adverse events is shown in Table 4.[36] It is important to regularly monitor patients for gastrointestinal adverse events that may be related to niraparib treatment, to allow early diagnosis and intervention. Label-recommended dose modifications for non-hematologic toxicities should be followed (Table 4).[20 37] Night-time administration of niraparib is a potential method for managing nausea/vomiting.[9 39] The prescribing clinician may also wish to consider the use of antiemetics such as metoclopramide, prochlorperazine, or promethazine 30 min before administration of PARP inhibitor, advise food 30–60 min before administration to prevent emesis, and/or prescribe benzodiazepines, steroids, or other drug interventions if needed.[14] Supportive care guidelines for anti-emesis management may provide additional strategies.[20] Dietary modifications and avoidance of large meals, as well as prescription of proton pump inhibitor therapies, tricyclic antidepressants, or prokinetics may be used to manage dyspepsia.[14]

Fatigue

Niraparib Trial Data

Fatigue was frequently reported for niraparib across studies in epithelial ovarian cancer with the incidence of any grade fatigue ranging from 25% to 59% (Online supplemental table 3).[3–6] However, most cases were mild: grade ≥3 fatigue ranged from 1% to 8% across studies[3–6] and, in the NOVA trial, had a median time to onset of 34 days and median duration of 17 days. Supportive treatment strategies including dose modifications occurred in <7% of patients (dose interuption 6%; dose reduction 5%); only 3% of patients in NOVA discontinued niraparib due to fatigue.[38]

Grading, Monitoring, and Management

Grading of fatigue is shown in Table 4, which also outlines monitoring and management recommendations.[36] Supportive interventions for fatigue might include exercise and physical fitness regimes, advice on conserving energy during everyday tasks, massage, cognitive behavioral therapy, and other mind-body approaches, as well as pharmacologic agents such as psychostimulants (eg, methylphenidate).[13] Fatigue can also be managed with dose modifications such as dose reductions and interruptions.[7]

Insomnia

Niraparib Trial Data

Insomnia (of any grade) was reported in 22–31% of patients across the studies and was generally low grade (grade ≥3 in ≤1% of patients; see Online supplemental table 3).[3–5]

Grading, Monitoring, and Management

Grading of insomnia is shown in Table 4, which also outlines monitoring and management recommendations.[36] Supportive interventions for insomnia might include sleep hygiene education, cognitive behavioral treatment, and/or pharmacologic approaches.[14]

Hypertension

Niraparib Trial Data

In PRIMA, 17% of patients receiving niraparib (vs 7% on placebo) experienced any-grade hypertension; the rate of grade ≥3 events was 6% and 1%, respectively.[3] Grade ≥3 hypertension was experienced by 5% of patients receiving an individualized starting dose of niraparib compared with 7% of patients receiving a fixed starting dose.[27] For the *BRCA* mutated cohort, the incidence of grade ≥3 hypertension was 9% and 2% with niraparib fixed starting dose and individualized starting dose, respectively, and 5% versus 7% for the *BRCA* wild-type cohort.[28 29] Retrospective analyses by age showed that grade ≥3 hypertension was lower in patients receiving niraparib who were aged ≥65 years compared with those <65 years of age (8% vs 5%, respectively) but similar in patients aged ≥75 and <75 years (6% vs 6%).[35] Notably, 37% of patients randomized to niraparib in the PRIMA trial had a history of hypertension (compared with 40% in the placebo arm). Hypertension is only reported as an adverse event in clinical trials if it worsens compared with baseline. Similar hypertension incidence was reported in the PRIME trial (17% for niraparib vs 6% for placebo; grade ≥3, 5% vs 0%).[6]

In NOVA, 19% of patients receiving niraparib (vs 4% on placebo) experienced any-grade hypertension adverse events and 8% of events were grade ≥3 (vs 2%).[4] Retrospective analyses showed that the incidence of hypertension was similar in patients aged ≥70 and <70 years of age (7% and 8%, respectively).[31] Overall, 31% of patients in the niraparib arm and 28% in the placebo arm had a history of hypertension; again, this was only reported as an adverse event if it worsened from baseline. In NORA, the incidence of any-grade hypertension was 11% with niraparib (1% grade ≥3) compared with 1% in the placebo arm (no grade ≥3 events).[5] In QUADRA, only 5% of patients receiving niraparib had hypertension reported as an adverse event (all grade 3 events)[3]; 54% had a history of hypertension.

Grading, Monitoring, and Management

Grading of hypertension is shown in Table 4.[36] Label recommendations for monitoring and management of hypertension (Table 4)[20 37] include determining patients had previously been diagnosed with hypertension or increased blood pressure, and whether they were prescribed antihypertensive agents. To monitor hypertension, blood pressure and heart rate readings should be taken at least weekly for the first 2 months, then monthly for the first year and periodically thereafter, irrespective of a medical history of hypertension. Patients with cardiovascular disorders should be monitored more closely, especially those with coronary insufficiency and cardiac arrhythmias. Hypertension can be managed with prescription of antihypertensive medications and adjustment of the niraparib dose as needed. Standard guidelines may be followed for the management of hypertension.[13 14]

Table 4 Non-hematologic adverse events grading and management

Non-hematologic*: Regularly monitor patients for gastrointestinal adverse events		
Adverse event	**Grade**	**Management**
Fatigue	Grade 1 Fatigue relieved by rest Grade 2 Fatigue not relieved by rest; limiting instrumental ADL Grade 3 Fatigue not relieved by rest; limiting self-care ADL Grade 4 NA	▶ Supportive interventions for fatigue might include exercise and physical fitness regimes, advice on conserving energy during everyday tasks ▶ Massage, cognitive-behavioral therapy, and other mind-body approaches ▶ Pharmacologic agents such as psychostimulants (eg, methylphenidate)
Nausea	Grade 1 Loss of appetite without alteration in eating habits Grade 2 Oral intake decreased without significant weight loss, dehydration, or malnutrition Grade 3 Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated Grade 4 NA	▶ Night-time administration of niraparib; use of anti-emetics 30 min before administration; intake of food 30–60 min before niraparib; benzodiazepines, steroids, domperidone, olanzapine, dronabinol, haloperidol, or scopolamine transdermal patch; consider supportive care guidelines on the management of anti-emesis[20]
Vomiting	Grade 1 Intervention not indicated Grade 2 Outpatient intravenous hydration; medical intervention indicated Grade 3 Tube feeding, TPN, or hospitalization indicated Grade 4 Life-threatening consequences	▶ Night-time administration of niraparib; use of anti-emetics 30 min before administration; intake of food 30–60 min before niraparib; benzodiazepines, steroids, domperidone, olanzapine, dronabinol, haloperidol, or scopolamine transdermal patch; consider supportive care guidelines on the management of anti-emesis[20]
Dyspepsia	Dyspepsia	▶ Dietary modification and avoiding large meals, proton pump inhibitor therapy, tricyclic antidepressants or prokinetics[14]
Hypertension	Grade 1 Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg Grade 2 Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg if previously within normal limits; change in baseline medical intervention indicated; recurrent or persistent (≥24 hour); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy initiated Grade 3 Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Grade 4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	▶ Ask patients if they have been diagnosed with hypertension or have had increased blood pressure in the past, and whether they are taking any antihypertensive agents ▶ Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during niraparib treatment ▶ Closely monitor patients with cardiovascular disorders, especially coronary insufficiency and cardiac arrhythmias ▶ Medically manage hypertension with antihypertensive medications ▶ Follow niraparib label-recommended dose modifications for non-hematologic toxicities[20 37] ▶ Refer to standard guidelines for the management of hypertension
Insomnia	Grade 1 Mild difficulty falling asleep, staying asleep, or waking up early Grade 2 Moderate difficulty falling asleep, staying asleep, or waking up early Grade 3 Severe difficulty in falling asleep, staying asleep, or waking up early Grade 4 NA	▶ Sleep hygiene education: advise patient to maintain sleep schedule, stay active throughout the day, avoid or limit naps, avoid or limit caffeine and alcohol, and refrain from using nicotine, manage painful conditions that may interfere with sleeping, avoid large meals and beverages before bed ▶ Cognitive behavioral therapy for insomnia is generally recommended as first-line treatment and is most often equal to or more effective than sleep medications ▶ Over-the-counter sleep aids are not intended for regular use, but consider whether antihistamine-containing products may cause unwanted drowsiness or additional adverse events (ie, dizziness, confusion, cognitive decline, difficulty urinating) ▶ Prescription sleeping medication can be prescribed, however only eszopiclone, ramelteon, zaleplon, and zolpidem are approved for long-term use (ie, more than a few weeks)[49]
Palpitations	Grade 1 Mild symptoms, intervention not indicated Grade 2 Moderate Grade 3 NA Grade 4 NA	▶ Review the patient's medical history ▶ Perform a physical examination for signs of medical conditions that can cause palpitations (ie, swollen thyroid gland); note: palpitations can also be a symptom of anemia ▶ If the palpitations are not caused by a medical condition, treatment is not usually prescribed. Instead recommend that patients avoid triggers which result in palpitations (eg, stress, stimulants (eg, caffeine), illegal drugs) ▶ If an arrhythmia or other heart condition is suspected, follow-on tests may include ECG, Holter monitoring usually for 24–72 hours, and echocardiogram ▶ Ask the patient to keep a diary of when palpitations occur

*For non-hematologic CTCAE grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment, withhold niraparib for a maximum of 28 days or until resolution of the adverse reaction; resume niraparib at a reduced dose. If the non-hematologic CTCAE grade ≥3 adverse reaction lasts >28 days while receiving niraparib 100 mg/day, discontinue niraparib.
ADL, activities of daily living; BP, blood pressure; NA, not applicable; TPN, total parenteral nutrition.

Palpitations

Niraparib Trial Data

In NOVA, palpitations were reported in 38 (10%) patients receiving niraparib and all reports were low grade (grade ≤2) in severity; four patients (1%) experienced treatment interruption and one patient (<1%) had dose reduction due to the event.[4] The incidence of palpitations among niraparib-treated patients was similar between *BRCA* mutated and non-*BRCA* mutated populations (9% and 11%,

respectively). Similarly, in the PRIME trial, 15% of patients reported palpitations with niraparib compared with 4% of patients receiving placebo; no grade 3 events were reported.[6] In PRIMA, a notable difference was observed in the overall incidence of palpitations between patients on a fixed starting dose and those on an individualized starting dose of niraparib (10% vs 4%, respectively).

Grading, Monitoring, and Management

Recommendations for monitoring and management of palpitations include reviewing the patient's medical history and ruling out other potential causes such as hyperthyroidism. If arrhythmia or other heart conditions are suspected as the cause of the palpitations, follow-up tests may include ECG, Holter monitoring for 24–72 hours, and an echocardiogram to identify any structural abnormalities or disruptions to blood flow.[40]

Related Considerations for Patient Care

Common adverse events associated with niraparib, including gastrointestinal symptoms and fatigue, are often associated with advanced ovarian cancer and can negatively impact QoL. Exacerbation of underlying symptoms should be avoided where possible.[15] Patients should be counseled on specific gastrointestinal adverse events that may occur and how to report them, so that supportive medications and niraparib dose modifications (as indicated) can be introduced early.

Patient-reported outcomes from the PRIMA trial have shown that patients with epithelial ovarian cancer receiving niraparib did not experience deterioration in their health-related QoL compared with placebo. Scores were comparable for niraparib and placebo regardless of age group (<65 or ≥65 years, or <75 or ≥75 years)[35] or *BRCA* mutation status in PRIMA.[28 29] Likewise, patients with recurrent disease treated with niraparib in NOVA had similar patient-reported outcomes as those receving placebo; there were no significant differences between treatment arms.[4]

In a post hoc analysis of NOVA data, hematologic toxicity (anemia, neutropenia, and thrombocytopenia) had no significant negative effect on health-related QoL.[18] Additionally, niraparib-treated patients in the PRIMA and NOVA trials experienced more time without symptoms or toxicities (TWiST),[17 41] demonstrating that patients receiving niraparib maintain good QoL. In NOVA, niraparib was beneficial in cohorts with and without germline *BRCA* mutations, respectively.

DISCUSSION

Patients with advanced epithelial ovarian cancer require effective management of adverse events to optimize duration of treatment, which ultimately has the potential to affect efficacy and QoL. Clinical trial experience with niraparib has shown that most adverse events can be managed through dose interruptions or dose reductions.[13] In PRIMA, the individualized starting dose improved the safety profile of niraparib with comparable efficacy to the fixed starting dose. In PRIME, adverse event rates were generally lower compared with PRIMA, potentially because all PRIME patients received an individualized starting dose. In the recurrent maintenance setting, adverse event rates appeared more favorable in the NORA study in which most patients received an individualized starting dose, compared with NOVA in which all patients received a niraparib fixed starting dose. However, caution should be exercised when comparing trials of different patient populations. In particular, both the PRIME and NORA trials were conducted in Chinese populations, and extrapolation of these data to European/US patient populations should be made with caution.

Our findings are reflected in real-world clinical practice. A US-based study of medical records for patients receiving niraparib 200 mg as maintenance therapy for recurrent epithelial ovarian cancer following platinum-based chemotherapy found that 37% experienced one or more of the three most common all-grade adverse events within 3 months of niraparib initiation: nausea (16% (grade 3/4, 2%)), thrombocytopenia (14% (grade 3/4, 3%)), and fatigue (24% (grade 3/4, 3%)).[42] The incidence of these adverse events was lower than that reported with a 300 mg starting dose of niraparib in NOVA.[42] A Norwegian-based retrospective multicenter study of niraparib in 106 patients with non-*BRCA* mutated platinum-sensitive recurrent epithelial ovarian cancer reported grade 3/4 hematologic events in 25% of patients, most commonly anemia (15%), thrombocytopenia (11%), and neutropenia (8%). Adverse events led to dose interruption in 38% and dose reduction in 44% of patients, but were significantly reduced in patients who received an individualized starting dose.[43] In a retrospective study of niraparib maintenance conducted within a Spanish expanded access program (n=316 patients; 80% had *BRCA* wild-type epithelial ovarian cancer), nearly two-thirds of patients (n=203; 64%) received an individualized starting dose. Common grade 3/4 hematologic adverse events were reduced with an individualized starting dose compared with a fixed starting dose, including thrombocytopenia (17% vs 32%), anemia (12% vs 18%), and neutropenia (8% vs 6%). There were no relevant grade 3/4 non-hematologic events and 6% of patients discontinued due to niraparib-related adverse events.[44]

Long-term safety data from clinical trials suggest that a longer duration of treatment with niraparib in epithelial ovarian cancer does not have a negative or cumulative effect on adverse events.[32 33] After approximately 4 months, patients appear to be stable at their appropriate dose.[32] Although secondary efficacy endpoints in the NOVA trial (final data cut-off October 2020) were not statistically powered, a trend towards improved survival was demonstrated with niraparib treatment compared with placebo in patients with a germline *BRCA* mutation based on adjusted analyses, with a 9.7-month increase in survival, indicating the benefit of niraparib maintenance therapy beyond first progression. Overall, the incidence of grade ≥3 adverse events typically decreased after the first year of niraparib treatment, suggesting that niraparib is well tolerated with appropriate management strategies; 13% of patients remained on niraparib for more than 3 years.[32 33] Additionally, a recent ad hoc interim analysis from the NORA trial of niraparib maintenance treatment using an individualized starting dose for patients with platinum-sensitive recurrent ovarian cancer (data cut-off September 2022) reported a potentially favorable trend in overall survival, irrespective of germline *BRCA* status.[45] Long-term progression-free survival (ad hoc analyses) reported from the updated PRIMA trial cut-off date (data cut-off November 2021) demonstrated a sustained and durable progression-free survival benefit in the overall population and across biomarker subgroups after a median follow-up of 3.5 years.[46] Long-term niraparib monotherapy was also associated with a low rate of treatment

discontinuation due to adverse events and the benefit of an individualized starting dose was reinforced with patients generally having a lower incidence of treatment-emergent adverse events.[46] Using PARP inhibitors can increase the chemotherapy-free interval for patients with epithelial ovarian cancer, with the potential to delay or avoid chemotherapy-associated toxicity.

Although similarities are evident in the safety profiles of niraparib and other PARP inhibitors such as olaparib, rucaparib, and veliparib, differences exist in the incidence and severity of some events.[39 47 48] Across pivotal niraparib trials, no new safety signals were identified. The incidence of thrombocytopenia observed with an individualized starting dose of niraparib was generally increased compared with other PARP inhibitor trials (SOLO1,[48] ARIEL3[40]). However, effective management is reflected by the small percentage of patients withdrawing from niraparib treatment due to thrombocytopenia events (PRIMA, 4.3%; NOVA, 1.9%).[3] Non-hematological events of nausea and vomiting were the most commonly reported gastrointestinal events across all niraparib trials, and are also commonly observed with other PARP inhibitors.[39 48] The incidence of nausea and vomiting with niraparib decreased over time and with an individualized starting dose regimen.[32] Notably, niraparib remains the only approved PARP inhibitor with once-daily dosing for patients with ovarian cancer, offering the potential to alleviate nausea and vomiting using night-time dosing.

CONCLUSIONS

Both clinical trial and real-world evidence suggest that niraparib has a predictable safety profile that is broadly similar to that for other PARP inhibitors. The incorporation of an individualized starting dose, along with supportive care and dose modifications, appears to mitigate adverse events without impairing niraparib efficacy. An individualized starting dose, if incorporated earlier in the treatment paradigm, could reduce the occurrence of some adverse events. Further, once-daily dosing of niraparib may benefit certain patients; night-time dosing may help alleviate gastrointestinal symptoms. Niraparib metabolism through carboxylesterases may potentially reduce drug–drug interactions compared with other PARP inhibitors. Overall, niraparib safety supports its selection as monotherapy treatment for patients with epithelial ovarian cancer.

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