



## Case series

# Pyridoxine for prevention and treatment of PARP inhibitor induced nausea and vomiting

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## ABSTRACT

Poly-ADP ribose polymerase inhibitors (PARPi) are a promising new treatment option for patients with ovarian cancer and are moderately emetogenic. Tolerance of therapy is paramount, and uncontrolled nausea and vomiting may limit use. Although most patients will experience improvement in nausea and vomiting after one to two months, approximately one in twenty patients will discontinue therapy due to unrelieved symptom burden.

Three cases of olaparib-related nausea and vomiting mitigated by primary pyridoxine use are reported. Case 1 demonstrates successful use of pyridoxine in breakthrough nausea. Case 2 details the use of pyridoxine following refractory nausea and vomiting requiring hospitalization. Case 3 describes a prophylactic approach for a patient with significant anticipatory nausea. All three patients tolerated olaparib after starting and continuing pyridoxine. Vitamin B6, or pyridoxine, was successful as both a therapeutic and prophylactic option for significant treatment-related nausea and vomiting with PARPi use.

## 1. Introduction

Ovarian cancer frequently has a genetic basis, and germline *BRCA1* and *BRCA2* mutations have been found in 18% of ovary, fallopian, and primary peritoneal carcinomas (Norquist et al., 2016). Diagnosis of *BRCA* germline and somatic mutations provide women with additional personalized cancer therapies such as poly-ADP ribose polymerase inhibitors (PARPi). Most recently, SOLO3, a randomized controlled trial comparing olaparib to chemotherapy in ovarian cancer patients with germline *BRCA* mutations, has demonstrated improved progression free survival with olaparib following two or more prior lines of platinum-based chemotherapy (Penson et al., 2019).

Common side effects of PARPi include fatigue, anemia, and gastrointestinal side effects. PARPi are moderately emetogenic, and tolerance is generally expected after one to two months of therapy (Pujade-Lauraine et al., 2017). Severe grade 3 or 4 nausea and vomiting are reported in up to 5%, see Table 1 (Prices, Coupons and Savings Tips [WWW Document], 2011); (Friedlander et al., 2016). Prophylactic antiemetics are recommended, and ondansetron is commonly recommended prior to PARPi use (Kristeleit et al., 2017); (Swisher et al., 2017). Additional anti-emetic therapies traditionally include olanzapine, dexamethasone, lorazepam, scopolamine, haloperidol, metoclopramide, phenothiazine, substance P inhibitors, and cannabinoids with careful consideration regarding the type of nausea experienced

(Gunderson et al., 2018). When these anti-emetics therapies are not successful, treatment interruption and dose reduction are recommended. Moore and Matulonis suggested discontinuing PARPi with a third interruption or lack of resolution by 28 days (Moore et al., 2018).

Chemotherapy induced nausea and vomiting may be categorized into the following types: acute, recurrent, refractory, anticipatory, and breakthrough (Navari and Aapro, 2016). Patients may have varied responses to the same chemotherapeutic agent, and often personalization of an anti-emetic strategy is required. The majority of clinically utilized anti-emetics are known to cause potential adverse reactions, including tardive dyskinesia, QTc prolongation, sedation, agitation, confusion, and drug interactions (Ettinger et al., 2007).

Pyridoxine is commonly used in obstetrics for management of pregnancy-related nausea and vomiting, and unlike traditional antiemetics, has few adverse effects (“ACOG Practice Bulletin No. 189,” 2018). Given the favorable side effect profile and low cost, off-label pyridoxine was provided to some patients receiving PARPi, including a group of women participating in SOLO3 at the University of Alabama at Birmingham after conventional anti-emetic strategies. In each instance, pyridoxine was effective, continued while on treatment, and allowed continued PARPi use. Importantly, participation in a clinical trial allowed objective assessment and documentation of the potential utility of pyridoxine per Common Terminology Criteria for Adverse Events

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**Table 1**

Summary of most common gastrointestinal side effects identified for those using olaparib based upon the [Common Terminology Criteria for Adverse Events \(2009\)](#) prospective assessment version 4; GERD – gastroesophageal reflux disease ([Ettinger et al., 2007](#)).

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation	Occasional symptoms	Regular symptoms	Requiring intervention	Life threatening	
GERD	Mild symptoms, no intervention	Medical intervention	Surgical intervention		
Nausea	Decreased appetite, normal intake	Decreased oral intake	Hospitalization, TPN, or feeding tube		
Vomiting	1–2 episodes in 24 h	3–5 episodes in 24 h	Hospitalization, TPN, or feeding tube	Life threatening	Death

Common Terminology Criteria for Adverse Gastrointestinal Events.

prospective assessments. All three patients have provided written consent for case presentation.

## 2. Case 1

The patient is a 55 year-old with stage IIIC mixed epithelial adenocarcinoma treated with optimal primary debulking followed by adjuvant combined intraperitoneal and intravenous platinum and taxane therapy with a 15 month disease free interval. Following recurrence, she had an optimal secondary cytoreduction followed by six cycles of pegylated liposomal doxorubicin and carboplatin. Prior to second disease recurrence, her platinum free interval was eight months.

At baseline, she reported grade 1 nausea, vomiting, diarrhea, and constipation. Due to significant breakthrough nausea following her first dose, despite prophylactic ondansetron, she was counseled to start pyridoxine 25 mg daily. Initially, she reported worsened grade 2 constipation. After two weeks of pyridoxine in place of ondansetron for nausea prophylaxis, she gained significant improvement in nausea, vomiting, and constipation. She continued olaparib with concurrent pyridoxine for five cycles until disease progression.

## 3. Case 2

The patient is a 42 year-old with stage IIIC high grade serous ovarian carcinoma treated with optimal primary debulking surgery followed by adjuvant combined intraperitoneal and intravenous platinum and taxane therapy. She received an additional 12 cycles of paclitaxel (135 mg/m<sup>2</sup> every 28 days) as part of GOG 212, a randomized controlled trial investigating maintenance therapy versus surveillance alone, in patients with advanced staged disease responding to primary therapy. After a platinum free interval of 53 months, she had a secondary optimal cytoreduction for isolated disease recurrence in the pelvis followed by adjuvant carboplatin. Following an additional platinum free interval of 32 months, she was diagnosed with a second recurrence with disease limited to an obturator lymph node and elected for participation in SOLO3.

Baseline pre-treatment toxicity data included grade 1 nausea, constipation, heartburn, and abdominal pain. She randomized to olaparib, and had worsening of constipation while utilizing ondansetron for nausea prophylaxis. After cycle three, her constipation worsened despite miralax and magnesium citrate. She began prochlorperazine and promethazine after cycle four, and unfortunately experienced significant motor dyskinesia.

Following cycle seven, she developed grade 3 nausea and vomiting requiring hospitalization. After hydration and supportive care, she initiated pyridoxine 25 mg twice daily as a potential final effort to continue olaparib. She experienced resolution of her abdominal pain and improvements in nausea, vomiting, and constipation. She reduced the use of additional anti-emetics and no longer required a bowel regimen to manage constipation. The patient remains on therapy with adverse events mitigated by continued pyridoxine use and has now completed 24 months of therapy without interruption.

## 4. Case 3

The patient is a 76 year-old with stage IVA high grade serous ovarian cancer treated with neoadjuvant platinum and taxane based chemotherapy secondary to a malignant pleural effusion, then had an optimal interval debulking surgery, and she completed adjuvant platinum and taxane chemotherapy. She had a 14 month platinum free interval until recurrence which was treated with pegylated liposomal doxorubicin and carboplatin. Her second recurrence was diagnosed eight months later.

Pre-treatment symptoms included grade 1 nausea, vomiting, constipation, diarrhea, and heartburn. Due to significant anticipation of worsening nausea and shared decision making focused on quality of life, she desired an alternative to conventional chemotherapy if side effects could be minimized. For this reason, she initiated pyridoxine 25 mg daily concurrently with olaparib to mitigate anticipatory nausea. By cycle 1 day 8, she had resolution of grade 1 vomiting and required ondansetron once weekly. After cycle eight, she no longer needed ondansetron, and in total she tolerated 16 monthly cycles of olaparib therapy with the continued use of pyridoxine until experiencing disease progression.

## 5. Conclusion

The decision for how to treat recurrent cancer is complex and relies upon patient preferences, potential therapeutic options, and tolerance of previous therapy among many considerations. Quality of life while receiving chemotherapy serves as an important balance with the goals of prolonging overall and progression free survival. In part, the advancement of chemotherapy is paced by the development of effective strategies to tolerate therapy.

Despite advances in anticancer treatment, it remains challenging to treat chemotherapy induced nausea and vomiting ([Natale, 2018](#); [Navari, 2015](#)). Pyridoxine, herein utilized as a 25 mg once or twice daily tablet to minimize patient burden and polypharmacy, was an effective and inexpensive means to mitigate refractory, breakthrough, and anticipatory chemotherapy induced nausea associated with olaparib in a subset of patients participating in a clinical trial with objective and regular adverse event ascertainment. The tolerance of therapy was improved with pyridoxine and did not require significant lifestyle or dietary changes. Pyridoxine 25 mg taken daily is approximately one-tenth the cost of generic ondansetron 4 mg used daily and potentially 300 times less expensive than name brand ondansetron 4 mg used daily ([www.goodrx.com](http://www.goodrx.com)).

The primary endpoint results from SOLO3 demonstrated an improvement in progression free survival advantage for germline *BRCA* mutated, recurrent epithelial ovarian cancer after two or more lines of platinum based chemotherapy compared to chemotherapy ([Penson et al., 2019](#)). Currently, there are four commercially available PARPi, with clinical applications becoming broader through personalized anticancer strategies ([Zimmer et al., 2018](#)). Given the high cost of PARPi, concerns for polypharmacy, and the growing complexities associated with tolerating chemotherapy, the potential future evaluation and utilization of pyridoxine with a PARPi may be a simple and beneficial intervention.

## Author contributions

Stuart A. Ostby, MD: Case review and manuscript writing.

Haller J. Smith, MD: Manuscript writing and revisions.

Charles A. Leath, III, MD, MSPH: Conceptual idea, manuscript writing, and revisions.

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## Disclosures

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