Case Report

First-Line PARP Inhibitors—Emerging Side Effects Require Caution: A Case of PARPi-Induced Pneumonitis

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ABSTRACT

Niraparib, an inhibitor of poly(adenosine diphosphate [ADP]-ribose) 1 and 2, has been shown to improve progression free survival in patients when used as maintenance treatment after first-line platinum-based chemotherapy in advanced stage (III to IV) high-grade ovarian cancer, and after platinum-based chemotherapy for relapsed disease. For grades greater than III, commonly reported side effects include bone marrow suppression (thrombocytopenia, neutropenia, and anemia) and hypertension. However, grade $\geq$ III pneumonitis was not reported in phase III trials (PRIMA or NOVA). We present a case of life-threatening niraparib-induced pneumonitis. With recent approval for use of first-line maintenance niraparib in the United States and Europe, knowledge of the side effects and how to manage them is vital.

Keywords: PARPi, niraparib, pneumonitis, case report

INTRODUCTION

In late 2017, the poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi) niraparib[1] was approved as maintenance treatment after platinum-based chemotherapy for relapsed high-grade epithelial ovarian, fallopian tube, and primary peritoneal cancer regardless of *BRCA 1/2* mutation status. It was later approved for maintenance treatment in the first-line setting regardless of *BRCA 1/2* mutation status. Although fatigue, bone marrow suppression, and vomiting are well-recognized side effects of PARPi[1–3] (olaparib, niraparib, and rucaparib), pneumonitis is rare. We present the case of a 58-year-old woman who developed grade IV bilateral pneumonitis (per Common Terminology Criteria for Adverse Events version 5.0.) while on niraparib maintenance therapy for relapsed platinum-sensitive high-grade serous ovarian cancer.

CASE

According to institutional policy, this report was exempt from ethical approval and informed consent was obtained from the patient to publish this case. The 58-year-old patient had no significant past medical history other than incidental moderate pulmonary emphysematous changes seen on staging computed tomography (CT) scans. She was an ex-smoker since 2015 with a 15-pack-year history. She had no symptoms suggestive of chronic obstructive pulmonary disease.

The patient was diagnosed with germline *BRCA* wild-type (gBRCAwt), stage IVa high-grade serous ovarian cancer in March 2017. She received six cycles of paclitaxel and carboplatin and operative complete cytoreduction.

Recurrence of high-grade serous ovarian cancer was confirmed biochemically (increase in CA-125 [cancer antigen 125] from a nadir of 9 to 115 kU/L) and radiographically in November 2018. The patient had 5 cycles of carboplatin AUC (area under the curve) of 5 and pegylated liposomal doxorubicin 30 mg/m^2. The sixth cycle was omitted owing to neutropenic sepsis after cycle five (albeit the patient had no infective symptoms). A CT of the chest, abdomen, and pelvis with contrast showed

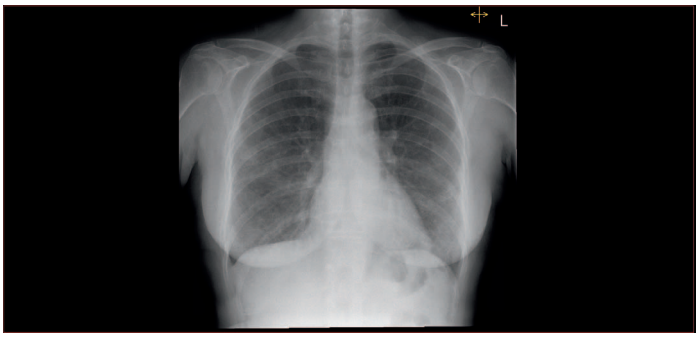

Figure 1.—A 58-year-old female presenting with exertional dyspnoea, pleuritic chest pain and cough due to niraparib-induced pneumonitis. x-ray taken at admission showing widespread patchy areas of increased air space opacification bilaterally.

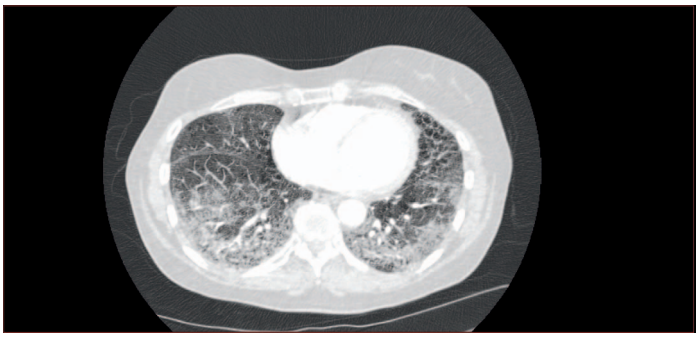

Figure 2.—A 58-year-old female presenting with exertional dyspnoea, pleuritic chest pain and cough due to niraparib-induced pneumonitis. Computed tomography pulmonary angiogram taken a day after admission and showing bibasal dependent ground-glass shadowing.

no evidence of disease after completion of chemotherapy, and CA-125 came down to 12 kU/L.

Eight weeks after chemotherapy, niraparib was commenced at 200 mg daily due to prior myelosuppression. After 3 weeks of niraparib, full blood count monitoring revealed CTCAE grade 2 thrombocytopenia (CTCAE: Common Terminology Criteria for Adverse Events version 5.0, US National Cancer Institute); therefore, niraparib was withheld for 3 weeks until the platelets had recovered sufficiently to recommence at 100 mg daily.

One week after restarting, the patient was admitted under oncology with a dry cough, exertional dyspnea, and pleuritic chest pain. On examination, there were fine bibasal crepitations and a new oxygen requirement of 2 L via nasal cannula to maintain saturations greater than 94%.

An electrocardiogram showed a sinus tachycardia; however, blood tests (including full blood count) and urea, electrolyte, and liver function tests were normal. C-reactive protein was raised at 84 mg/L. Sputum polymerase chain reaction was negative for influenza A/B, respiratory syncytial virus, adenovirus, *Mycoplasma pneumonia,* parainfluenza types 1–4, rhinovirus, coronavirus, metapneumovirus, cytomegalovirus, and *Pneumocystis jirovecci*. A chest X-ray (CXR) (Fig. 1) showed widespread patchy areas of opacification. A CT pulmonary angiogram (Fig. 2) was performed the day after admission and showed changes consistent with an organizing pneumonia superimposed on emphysematous lung.

The patient was started on clarithromycin and amoxicillin orally for presumed community-acquired pneumonia. Niraparib was withheld. Initial suspicion was this was unlikely to be drug-induced pneumonitis because, on review of medications at admission (including niraparib), none were listed in the summary of product characteristics or on Pneumotox (a database of drugs known to have caused drug-induced and iatrogenic respiratory disease). The patient had relatively little exposure to niraparib, and there was an alternative working diagnosis of community-acquired pneumonia.

The patient did not improve, and despite escalation of antibiotics to piperacillin-tazobactam, 10 days into admission the patient developed compensated type II respiratory failure (P_{CO_2} 6.0 kPa, P_{O_2} 5.1 kPa, H+ 38 nmol/L). The patient was transferred to level two care under the respiratory team and given high-flow nasal oxygen. The patient was not well enough at this point to obtain a tissue sample using open lung biopsy or bronchoscopy. A repeat CXR showed predominantly peripheral bilateral reticulation within the mid and lower zones, which had developed since the previous CXR. The decision was made to start intravenous methylprednisolone, at a dose of 1 mg/kg daily. Co-trimoxazole was also started in case this represented a *Pneumocystis jirovecci* pneumonia; however, multiple sputum samples were negative.

Pulsed methylprednisolone was given intravenously on 3 consecutive days. With these measures, the patient's oxygen requirement dropped rapidly, and she was stepped down to the ward. The patient was then started on oral prednisolone at 60 mg once daily (OD), and this was reduced by 5 mg every 4 days to 10 mg OD. A high-resolution chest CT performed 10 days after commencing steroid treatment showed improved appearances, but there was persisting ground-glass opacity, predominantly in the lower zones, and areas of irregular dilated bronchi (Fig. 3). An echocardiogram showed normal ventricles, with an ejection fraction of 50% to 55%. Antinuclear antibodies and antiglomerular base-

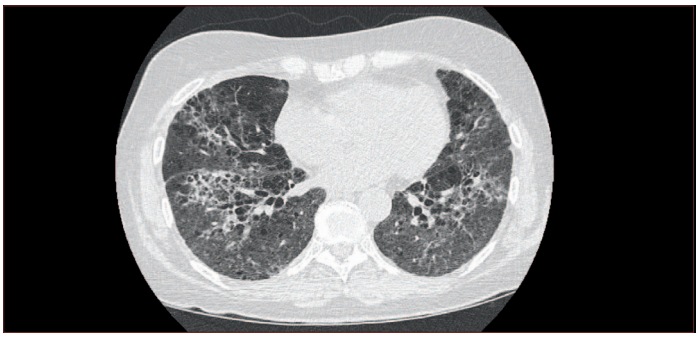

Figure 3.—A 58-year-old female presenting with exertional dyspnoea, pleuritic chest pain and cough due to niraparib-induced pneumonitis. High-resolution computed tomography taken 10 days into admission and showing dilated and irregular bronchi within the ground-glass opacity.

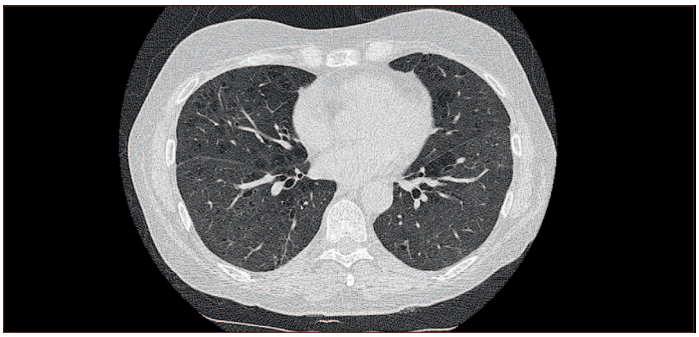

Figure 4.—A 58-year-old female presenting with exertional dyspnoea, pleuritic chest pain and cough due to niraparib-induced pneumonitis. High-resolution computed tomography taken 5 months after admission and showing almost complete resolution of ground-glass changes and airway dilatation in the lower zones.

ment membrane antibodies were negative, and MPO antibodies, PR3 antibodies, and C3 and C4 levels were within normal limits. After 27 days in the hospital the patient was discharged. Follow-up with the patient 2 weeks later revealed improvement in symptoms, oxygen saturations in the high 80s on room air, and an FEV1 (forced expiratory volume in 1 second) of 1.8 L (80% predicted) and FVC (forced vital capacity) of 2.13 L (79% predicted). A follow-up CXR showed persistent but improved opacification within the lung fields. The patient continued on 10 mg OD of prednisolone orally for another month. After a further month, there was improvement in the ground-glass shadowing, but there was evidence of chronic reticular change in the mid and upper zones in keeping with development of pulmonary fibrosis. Oxygen saturations at this point were 97% on room air, and prednisolone was weaned to stop over the next 3 months. A follow-up high-resolution chest CT scan taken 6 months later showed almost complete resolution of previous ground-glass opacification (Fig. 4).

DISCUSSION

Drug-induced pneumonitis, or drug-induced interstitial lung disease is a serious and potentially life-threatening adverse effect with over 350 known causative drugs.[4] It is defined as clinical and radiologic features consistent with interstitial lung disease after exposure to a drug, in the absence of an alternative cause, and with improvement on withdrawal of the offending drug. Given the challenges in diagnosis, drug-induced pneumonitis is not often identified as an adverse effect until late in drug development or after launch.[4]

Pneumonitis is a well-recognized adverse effect of many anticancer therapies. Checkpoint inhibitors have an incidence of up to 7%.[5] This tends to be an "on target" effect. "Off target" pneumonitis has also been reported with epidermal growth factor receptor inhibitors, and anaplastic lymphoma kinase receptor inhibitors.[6] Therefore, when introducing new therapies, it is important to identify causative agents early in development to allow safe design of combination regimens, as well as protocols for investigating and managing pneumonitis.

There have been a few reported cases of pneumonitis associated with PARPi; however, it is unclear if this is a class effect. Pneumonitis has been shown to be a rare but serious side effect of olaparib therapy with an incidence of less than 1%.[2] In a phase I trial of niraparib monotherapy,[7] at a dose of 60 mg daily, one patient developed a dose-limiting toxicity of grade III pneumonitis. Beyond this, in further phase III trials[8,9] there were no cases of grade $\geq$ III pneumonitis. To date, there have been no reported cases of rucaparib-associated pneumonitis; however, with increasing use of PARPi we may see more cases and be able to determine if pneumonitis is a class effect.

A mechanism of action by which PARPi may cause pneumonitis is unclear. PARP-1 is known to promote a proinflammatory response by positively regulating nuclear factor κ-B, which goes on to induce the production of proinflammatory cytokines, including tumor necrosis factor-a and interleukin-1B.[10] PARP-1 activation also inhibits interleukin-10 expression and Foxp3, which mediate inflammatory response. In vitro, inhibitors of PARP-1 have been shown to enhance the suppressive function of Treg cells through their promotion of Foxp3 stabilization.[11] Although PARP-1 has been implicated in Th1- and Th2-mediated inflammatory response,[10] PARP-1 depletion enhanced the severity of inflammation in an animal model of psoriasis. PARP-1 levels were also found to be lower in human samples of skin from psoriatic lesions.[12] Psoriasis is a Th17-mediated inflammatory response, and so PARP-1 may play a different function in this to Th1 and Th2 responses. If this is a class response, rather than specific to certain PARPi, this will influence decisions regarding rechallenging patients with alternative PARPi after PARPi-induced pneumonitis.

Determining the best treatment for drug-induced pneumonitis is challenging because there are no large randomized controlled trials comparing treatment strategies. As well as drug cessation, corticosteroids are also often used. The efficacy of corticosteroids varies significantly depending on the drug cause of the pneumonitis, underlying medical conditions, and dose of corticosteroid.[4] Organizing pneumonia is characterized by a brisk clinical response to high-dose corticosteroids, and in this case the effect of high-dose corticosteroid treatment was dramatic with rapid weaning of oxygen requirements.

CONCLUSION

This case report is the first real-world example of life-threatening pneumonitis induced by niraparib that can be found in the literature. Although this is a rare occurrence, in a patient presenting with dyspnea, cough, or hypoxia, pneumonitis should be considered in the differential diagnosis; changes in keeping with pneumonitis may be seen radiologically. Cessation of treatment,

input from respiratory physicians, and elimination of other causes followed by high-dose steroids should be considered to ameliorate symptoms. Close follow-up is also necessary because a minority of patients will go on to develop chronic fibrotic change.

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Corrigendum

Correction Notice for "First-Line PARP Inhibitors—Emerging Side Effects Require Caution: A Case of PARPi-Induced Pneumonitis" by McLaren et al

Correction Notice for "First-Line PARP Inhibitors—Emerging Side Effects Require Caution: A Case of PARPi-Induced Pneumonitis" by McLaren et al. *J Immunother Precis Oncol*. 2021; 4:175. DOI: 10.36401/JIPO-21-CX3.

In the article, "First-Line PARP Inhibitors—Emerging Side Effects Require Caution: A Case of PARPi-Induced Pneumonitis," by Alistair McLaren, Douglas Cartwright, Ewen Ross, and Patricia Roxburgh (Journal of Immunotherapy and Precision Oncology. Published online April 15, 2021. https://doi.org/10.36401/JIPO-20-33), the text states that pneumonitis is not listed as a side effect in the summary of product characteristics for niraparib. On April 23, 2021, the manufacturer of the branded niraparib product, Zejula (GlaxoSmithKline, GSK), informed the editors that pneumonitis was added to the summary of product characteristics for niraparib in July 2020. GSK shared that "Trial publications generally only report incidence of key side effects with incidence above 5-10% and therefore this rare side effect may have been missed in peer review material." Therefore, the following corrections have been made in the article.

In the Abstract, the third sentence, "However, pneumonitis is not listed as a side effect in the summary of product characteristics, or reported in phase III trials (PRIMA or NOVA)," has been corrected to "However, grade $\geq$ III pneumonitis was not reported in phase III trials (PRIMA or NOVA)."

In the Introduction, the third sentence, "Although fatigue, bone marrow suppression, and vomiting are well-recognized side effects of PARPi[1–3] (olaparib, niraparib, and rucaparib), pneumonitis is rare, being reported only in the summary of product characteristics for olaparib.[2]" has been corrected to "Although fatigue, bone marrow suppression, and vomiting are well-recognized side effects of PARPi[1–3] (olaparib, niraparib, and rucaparib), pneumonitis is rare."

In the Discussion, third paragraph, the fourth sentence, "Beyond this, in further phase III trials[8,9] there were no cases of pneumonitis" has been changed to "Beyond this, in further phase III trials[8,9] there were no cases of grade $\geq$ III pneumonitis."

In the Conclusion, the first sentence, "This case report is the first real-world example of pneumonitis induced by niraparib that can be found in the literature," has been corrected to "This case report is the first real-world example of life-threatening pneumonitis induced by niraparib that can be found in the literature."