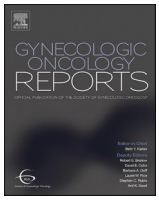
Gynecologic Oncology Reports 49 (2023) 101258

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



Case series

Tumor lenvatinib addiction and withdrawal rebound response in patients with advanced endometrial cancer

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ARTICLE INFO

Keywords:
Endometrial cancer
Lenvatinib
Pembrolizumab
Lenvatinib addiction
Rebound response

ABSTRACT

Combination therapy of lenvatinib, a multitargeted tyrosine kinase inhibitor (TKI), plus pembrolizumab, a monoclonal antibody targeting programmed death receptor 1 (PD-1), was recently approved by the Food and Drug Administration for therapy of advanced endometrial cancer. This case series highlights three patients with endometrial serous carcinoma who experienced disease stabilization or slow progression on lenvatinib plus pembrolizumab followed by rapid symptomatic growth of disease after lenvatinib discontinuation, and subsequent repeated response and symptom resolution after lenvatinib re-initiation. All patients died of disease complications 3 to 10 months after retreatment with lenvatinib. These observations highlight an important phenomenon of lenvatinib withdrawal rebound, likely driven by oncogenic signaling pathways upregulated in response to lenvatinib therapy. The findings of this case series represent a potential area for further research into the underlying mechanism for rebound and repeated response to lenvatinib, as well as strategies to mitigate disease flare related to lenvatinib withdrawal.

1. Introduction

After decades of decline, the incidence of endometrial cancer in the United States is now on the rise (Cote et al., 2015). Although the 5-year survival rate for localized disease is favorable, estimated at approximately 96%, patients with regional and distant metastases have significantly lower survival rates—71% and 20%, respectively (Survival Rates, 2022). Currently, standard-of-care treatment for advanced, recurrent, and metastatic endometrial carcinoma is carboplatin plus paclitaxel. However, recent advances in targeted therapy have expanded the treatment options for this patient population.

Lenvatinib is a multitargeted tyrosine kinase inhibitor (TKI) that targets various angiogenesis factors, including vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor (PDGF) receptor-alpha, RET, and KIT (Ott et al., 2017; Kato et al., 2016; Kimura et al., 2018). As single-agent therapy, lenvatinib has demonstrated an overall response rate (ORR) of 14.3% in patients with advanced endometrial cancer (Vergote et al., 2020). Pembrolizumab is a monoclonal antibody that targets programmed death receptor 1 (PD-1). While pembrolizumab alone has shown limited activity in mismatch repair-proficient (pMMR) endometrial cancer (Ott et al., 2017), the combination of lenvatinib plus pembrolizumab has shown increased efficacy in preclinical mouse studies, prompting the study of this combination in clinical trials (Kato et al., 2016; Kimura et al., 2018). The findings of KEYNOTE-146, a phase Ib/II study evaluating the combination of lenvatinib plus pembrolizumab in pre-treated, advanced endometrial cancer, demonstrated an objective response rate of 37.2% in patients with microsatellite stable (MSS)/pMMR endometrial cancer, with a progression-free survival (PFS) of 7.4 months and an overall survival (OS) of 16.4 months (Taylor et al., 2020). The findings of KEYNOTE-775, a phase III clinical trial comparing lenvatinib/pembrolizumab versus doxorubicin/paclitaxel in advanced, metastatic, or recurrent endometrial cancer that had progressed on a platinum-based regimen, demonstrated significantly longer PFS and OS in the lenvatinib/pembrolizumab arm, establishing the regimen as a standard-of-care second-line therapy for advanced endometrial cancer (Makker et al., 2022).

Patterns of response and resistance to lenvatinib/pembrolizumab

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https://doi.org/10.1016/j.gore.2023.101258
Received 8 June 2023; Received in revised form 2 August 2023; Accepted 5 August 2023
Available online 11 August 2023

therapy have not been well characterized. In this case series, we discuss three patients with endometrial serous carcinoma who experienced disease stabilization or slow progression on Lenvatinib/pembrolizumab followed by rapid symptomatic growth of disease after lenvatinib discontinuation, and subsequent repeated response and symptom resolution after lenvatinib re-initiation, though with disease progression and death within 3–10 months. All clinical information was obtained under an IRB-approved retrospective research protocol with patient consent.

1.1. Case 1

A 71-year-old patient presented with postmenopausal bleeding and was diagnosed with endometrial carcinoma after an endometrial biopsy. She did not have preoperative imaging for staging purposes. She underwent a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and tumor debulking to complete gross resection at an outside institution. Final pathology was notable for at least stage IIIC1, International Federation of Gynecology and Obstetrics (FIGO) tumor grade 3 endometrial carcinoma with ambiguous mixed features, invading full thickness myometrium and into the serosa, tumor positive for lymphovascular space invasion, bilateral ovarian involvement, right pelvic lymph node involvement, and sigmoid nodule involvement. Tumor-normal gene panel mutational profiling showed indeterminate microsatellite instability and an oncogenic somatic mutation in *TP53*. Postoperative computed tomography (CT) demonstrated innumerable metastatic pulmonary nodules, a 4.5-cm hepatic capsular implant, and an enlarged paraaortic lymph node. She was initiated on carboplatin and paclitaxel chemotherapy, but upon completion of six cycles experienced progression of disease at all metastatic sites. She was then started on lenvatinib plus pembrolizumab, 5 months after her initial debulking surgery. A surveillance scan at 3 months after initiation of lenvatinib/pembrolizumab demonstrated some response in her abdominopelvic lymphadenopathy, peritoneal implants, and pulmonary metastases (Fig. 1). The response was maintained at the 6-month scan, with slight enlargement of one of the liver metastases. After 6 months of lenvatinib/pembrolizumab, she tested positive for influenza A and was held off lenvatinib for approximately 12 days while recovering. Several days after stopping lenvatinib she presented to the emergency room with pain and was found to have marked disease progression, with new *peri*-hepatic, peritoneal, and cervical spine metastases (Fig. 1). She was restarted on lenvatinib/pembrolizumab and received palliative radiation therapy to her spine. A 1-month follow-up scan demonstrated treatment response with decrease in intraabdominal disease burden as well as treatment effect in the irradiated cervical spine osseus lesion (Fig. 1). Unfortunately, several weeks after her last radiation treatment, she presented with bowel perforation, which ultimately led to transition to hospice care. Of note, she did not have appreciable bowel disease on imaging prior to her presentation with bowel perforation. She had significant cancer progression within a short interval while off treatment and died of disease-related complications 15 months after her initial diagnosis, 10 months after initiation of second-line treatment with lenvatinib/pembrolizumab, 3 months after treatment re-initiation.

1.2. Case 2

A 66-year-old patient presented with postmenopausal bleeding. Transvaginal ultrasound and pelvic magnetic resonance imaging (MRI) demonstrated an ill-defined mass in the uterine cavity. She underwent a hysteroscopy and dilation and curettage, with final pathology demonstrating high-grade endometrial carcinoma. She then underwent a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, bilateral sentinel lymph node biopsy, and omental biopsy. Final pathology demonstrated stage IB uterine serous carcinoma with 9/15 mm myometrial invasion, suspicious lymphovascular invasion, and posterior lower uterine segment involvement. She underwent 6 cycles of postoperative carboplatin/paclitaxel. Thirteen months after completion of chemotherapy, she experienced recurrence in the peritoneal cavity as well as possible metastatic disease in the lungs. She was started on lenvatinib/pembrolizumab and achieved therapeutic response after 2 months on therapy (Fig. 2). After 5 months of combination therapy, she developed worsening painful palmar-plantar erythrodysesthesia and was held off lenvatinib for 10 days. She then presented to the hospital with worsening abdominal pain, distension, and constipation. CT of the abdomen and pelvis revealed markedly increased peritoneal carcinomatosis and large abdominal ascites, with rapid rise in serum CA-125 (Fig. 2). Due to apparent disease progression, the patient's therapy was switched to weekly paclitaxel. Despite this transition, the patient continued to exhibit rapidly re-accumulating ascites requiring multiple paracenteses. Six weeks after starting paclitaxel, the patient was restarted on lenvatinib. Within a week of restarting lenvatinib, she experienced decreasing abdominal distention and lower extremity swelling, with ultimate resolution of symptoms. A CT scan performed 2 months after restarting lenvatinib demonstrated response, with decreased peritoneal carcinomatosis and ascites (Fig. 2). Eventually, due to recurrent palmar-plantar erythrodysesthesia, the patient

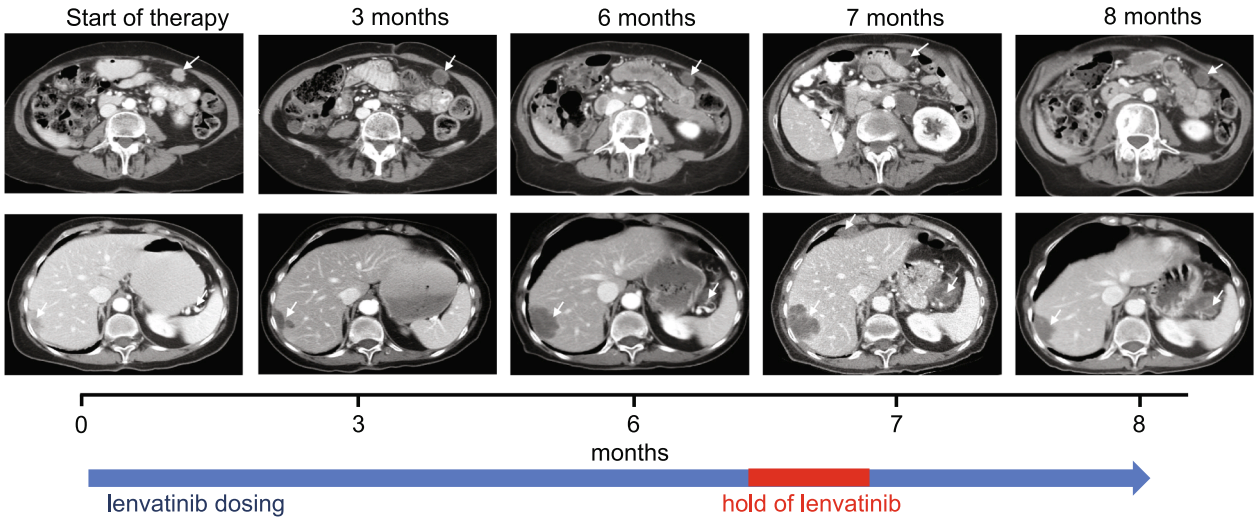

Fig. 1. Course of lenvatinib/pembrolizumab therapy for case 1. Representative computed tomography images for longitudinal disease monitoring. Arrows point to representative disease sites.

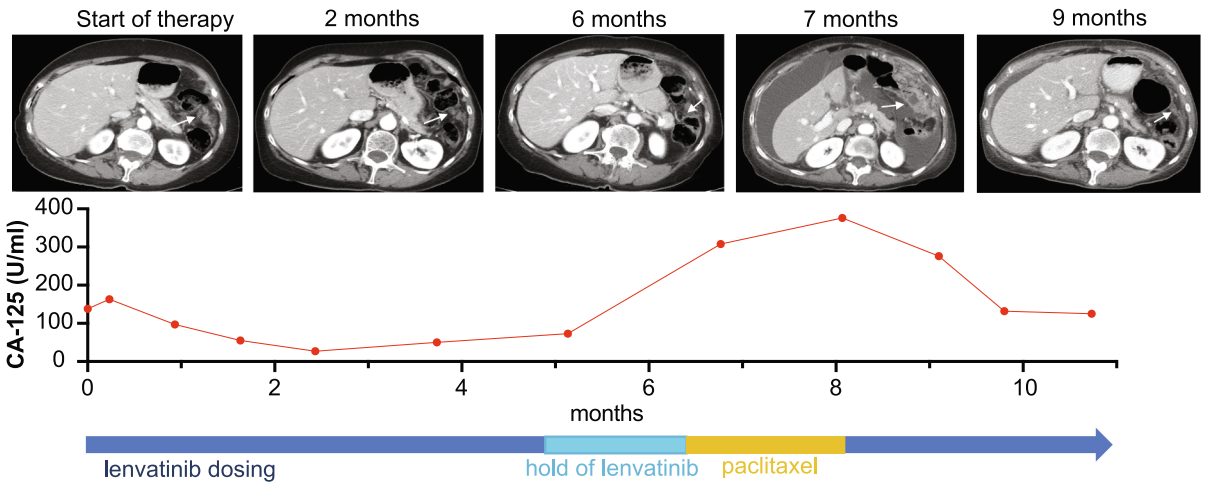

Fig. 2. Course of lenvatinib/pembrolizumab therapy for case 2. Top: representative computed tomography images. Bottom: CA-125 measurements over time, with corresponding lenvatinib treatment timeline.

once again was held off lenvatinib for 3 days, which was accompanied by rapid worsening of her abdominal distention and symptoms. Following re-initiation of lenvatinib, the patient was hospitalized for spontaneous bacterial peritonitis, possibly secondary to bowel perforation. At this time, imaging demonstrated moderate volume ascites and unchanged peritoneal carcinomatosis when compared to 3 months prior. After discharge from the hospital, the patient's therapy was transitioned to paclitaxel with trastuzumab. Unfortunately, her clinical condition declined shortly after, with rapid accumulation of ascites. She died of disease-related complications 31 months after initial diagnosis, 14 months after initiation of lenvatinib/pembrolizumab, 5 months after therapy re-initiation.

1.3. Case 3

A 64-year-old patient presented with postmenopausal bleeding and endometrial irregularity on imaging. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy at an outside institution with final pathology revealing stage IA serous carcinoma arising from an endometrial polyp, though complete surgical staging was not performed. She underwent three cycles of carboplatin/paclitaxel, whole pelvic radiation, and vaginal brachytherapy. She had an 18-month progression-free interval, at which point a CT scan revealed peritoneal carcinomatosis. After biopsy confirmation of recurrent endometrial carcinoma, she presented to our institution for treatment and was started on lenvatinib/pembrolizumab. Two months after initiation of this regimen, radiologic response demonstrated decreased peritoneal carcinomatosis and ascites, which was maintained per a 5-month scan (Fig. 3). Two weeks following the 5-month scan, she developed acute abdominal pain and was held off lenvatinib for 1 week. She was ultimately diagnosed with acute cholecystitis, as well as increased ascites, on her 5.5-month scan (Fig. 3). The patient underwent cholecystostomy tube placement and continued to be held off lenvatinib. Several days later, the patient developed large-volume ascites, which required paracentesis. She was switched to weekly paclitaxel therapy but continued to reaccumulate ascites, requiring weekly paracenteses. After 6 weeks of paclitaxel therapy, due to persistent ascites, the patient was restarted on lenvatinib/pembrolizumab. Within several days of restarting lenvatinib, her symptoms improved, with complete resolution of ascites after 1 month. After approximately 4 months, she developed disease progression with re-accumulation of ascites. She was started on weekly paclitaxel plus trastuzumab for confirmed human epidermal growth factor receptor 2 (HER2) positivity by immunohistochemistry of the primary endometrial carcinoma, with a taper of lenvatinib for 3 weeks prior to complete discontinuation. She ultimately required intraperitoneal catheter placement to address her recurrent ascites. Of note, due to

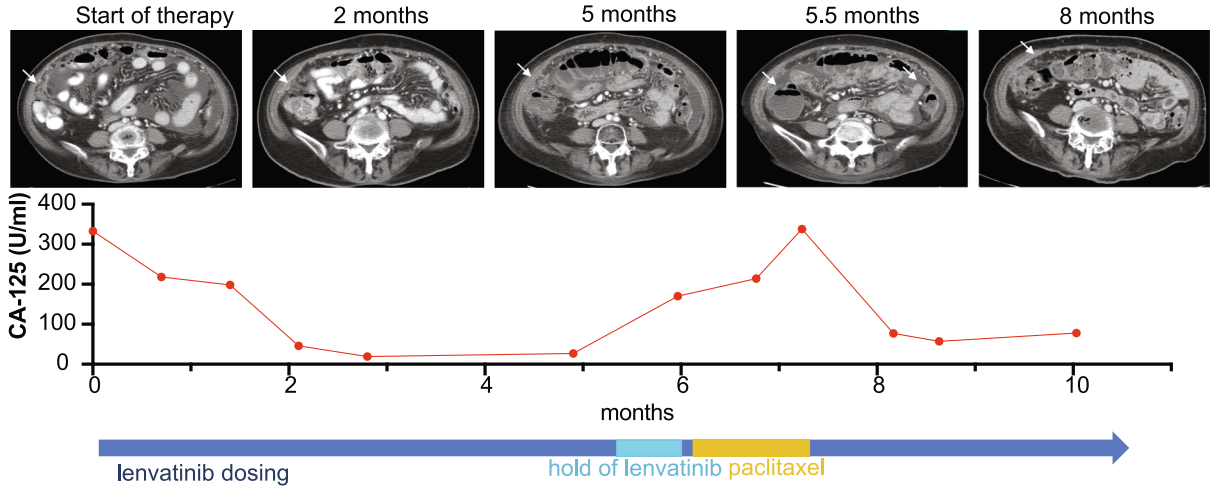

Fig. 3. Course of lenvatinib/pembrolizumab therapy for case 3. Top: representative computed tomography images. Bottom: CA-125 measurements over time, with corresponding lenvatinib treatment timeline.

persistent ascites, 3 months after switching to the paclitaxel/trastuzumab regimen, the patient self-resumed low-dose lenvatinib and once again experienced ascites resolution. She ultimately died of disease-related complications 3.5 years after initial diagnosis, 15 months after initiation of lenvatinib/pembrolizumab, 10 months after treatment re-initiation.

2. Discussion

In this case series, we describe tumor progression after discontinuation of lenvatinib/pembrolizumab combination therapy, as well as marked repeated response after restarting lenvatinib in at least 2 of our 3 patients, a phenomenon we have termed "lenvatinib addiction." In some patients, lenvatinib discontinuation can lead to rapid disease growth; however, re-treatment with lenvatinib can lead to repeated response and symptom improvement even with evidence of prior disease progression on lenvatinib/pembrolizumab. It is important to note that this re-treatment led to bowel perforations in 2 of the 3 patients with a fairly short survival time after reinitiation of treatment.

The exact mechanism of "lenvatinib addiction" is unknown. A potential mechanism of TKI withdrawal response may be related to increased accumulation of membrane receptors as a result of pharmacologic kinase inhibition as well as the rebound re-phosphorylation effect as described in a preclinical study of MET inhibitor withdrawal by Pupo et al. (2016) Oncogene addiction has also been described in a case report and a descriptive study looking at patients with *EGFR*-mutant lung cancer who experienced disease flare after discontinuation of TKIs as part of a clinical trial (Chaft et al., 2011; Kuriyama et al., 2013). Given the findings from these studies and our case series, in the patients with rapid symptomatic progression after lenvatinib discontinuation it may be prudent to consider a taper or even transition to a different targeted agent to combat the underlying biologic mechanisms of the withdrawal response to mitigate the disease flare effect. It is important to recognize that taper or transition to another TKI may be difficult in event of an acute event such as a bowel perforation such as experienced by 2 of our patients.

A crucial limitation of our case series was our inability to assess durability of response upon re-initiation of lenvatinib. Our first two cases demonstrated short response periods due to complications of bowel perforation. The third patient suffered clinically significant gastrointestinal bleeding from a duodenal ulcer after self-resuming lenvatinib. Although rare, gastrointestinal tract perforation is a potentially lethal consequence of antiangiogenic therapies such as lenvatinib (Date et al., 2018; Suzuki et al., 2020; Valerio et al., 2021). The potential for significant adverse events related to VEGF-targeted therapies questions the safety of lenvatinib for long-term use. Our findings present a potential area for further research into the underlying mechanisms of repeated response to lenvatinib as well as strategies to mitigate disease flare related to lenvatinib withdrawal.

Funding

The study was supported in part by a National Cancer Institute/National Institutes of Health Cancer Center Support Grant (P30 CA008748). B.W. is funded in part by Cycle for Survival and Breast Cancer Research Foundation grants.

CRediT authorship contribution statement

Clarissa Lam: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Debra Sarasohn:** Data curation, Visualization, Writing – review & editing. **Britta Weigelt:** Formal analysis, Visualization, Writing – review & editing. **Dmitriy Zamarin:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

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