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CASE REPORT

New treatment options for advanced endometrial carcinoma Special Issue

Overcoming disease progression in advanced endometrial cancer: a clinical case of sequential therapies

Amedeo Cefaliello[1,2], Angela Grieco[2], Roberto Buonaiuto[2,3], Valeria Forestieri[2]

[1]Department of Woman, Child and Public Health, Fondazione Policlinico Universitario 'A. Gemelli' IRCCS, Rome, Italy; [2]Division of Medical Oncology, Department of Clinical Medicine, University of Naples Federico II, Naples, Italy; [3]Scuola Superiore Meridionale (SSM), Clinical and Translational Oncology, Naples, Italy

Abstract

Immunotherapy has revolutionized the treatment landscape for solid tumours. Here, we describe the case of a 69-year-old woman with advanced endometrial cancer (EC) who achieved prolonged disease control with immunotherapy. The patient was diagnosed with stage IIIC EC in February 2020 and was treated with carboplatin and paclitaxel, followed by radiotherapy. Relapses occurred in February 2021 (treated with doxorubicin and palliative radiotherapy) and July 2022 (treated with a carboplatin rechallenge). Pembrolizumab and lenvatinib were started in November 2022. Although the initial scan showed progressive disease, restaging 2 months later showed stable disease, which was maintained on pembrolizumab and lenvatinib until progression in October 2024.

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Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy, predominantly affecting postmenopausal women.[1] Although most cases are diagnosed at an early stage and generally carry a favourable prognosis, approximately 15–20% of patients present with advanced or recurrent disease, which is associated with poor clinical outcomes and limited treatment options. Conventional therapies, such as cytotoxic chemotherapy and radiotherapy, often offer limited efficacy in these settings, highlighting the urgent need for novel therapeutic strategies.[2,3]

Immunotherapy has emerged as a transformative treatment modality in oncology, offering new hope for patients with advanced or refractory cancers.[4] Immune-checkpoint inhibitors (ICIs), such as pembrolizumab, have demonstrated remarkable clinical activity, particularly in tumours with microsatellite instability-high or mismatch repair deficiency, which are characterized by high mutational burdens and increased immunogenicity. However, the majority of EC tumours are mismatch repair proficient (pMMR) or microsatellite stable, and demonstrate limited responsiveness to ICIs as monotherapy, making combination strategies essential to improving therapeutic outcomes.

The combination of pembrolizumab with lenvatinib, a multi-targeted tyrosine kinase inhibitor, represents a significant advancement in the management of pMMR EC. Lenvatinib exerts its effects by targeting pathways such as VEGFR and FGFR, altering the tumour microenvironment and potentiating the immune system's response to ICIs.[5] This regimen has been approved for use in advanced, previously treated EC and has shown encouraging efficacy in clinical trials, even in challenging clinical contexts.

In this article, we present a case demonstrating the use of combination immunotherapy with pembrolizumab and

lenvatinib in a patient with recurrent and metastatic EC. This case highlights key aspects of treatment response, the management of adverse events and the evolving disease course under immunotherapy.

Case report

Consent for publication: The patient signed informed consent for the publication of data and any related images.

A 69-year-old woman presented in September 2019 with vaginal bleeding. Diagnostic evaluation, including ultrasound, identified an irregularly marginated lesion measuring 2 × 3 cm at the uterine isthmus. A CT scan suggested that the disease was confined to the uterus. The patient subsequently underwent a total hysterectomy with bilateral salpingo-oophorectomy, along with pelvic and para-aortic lymph node sampling. Histopathological analysis confirmed endometrioid adenocarcinoma, classified as pT1b N1a, FIGO stage IIIC. The tumour was p53 wild-type and was demonstrated to be pMMR.

From December 2019 to February 2020, the patient received adjuvant therapy consisting of four cycles of carboplatin (AUC dose of 5) and paclitaxel (175 mg/m²), followed by external beam radiation therapy to the pelvic region. Post-treatment follow-up remained uneventful until February 2021.

In February 2021, a follow-up CT scan revealed disease recurrence, with lymph node involvement in the intercaval and para-aortic regions, along with a bone metastasis in the right iliac wing. Due to significant pelvic pain (Numeric Rating Scale 8/10), the patient underwent palliative radiotherapy to the pelvic bone lesion, receiving a total dose of 30 Gy delivered in 10 fractions. Additionally, denosumab 120 mg every 28 days was initiated to prevent skeletal-related events. On February 2021, the patient began second-line treatment with pegylated liposomal doxorubicin at a dose of 40 mg/m². A total of eight cycles were administered through September 2021, during which the disease remained stable.

In July 2022, the patient experienced further disease progression, with new lesions identified in the pulmonary region. This prompted the initiation of third-line therapy with carboplatin (AUC dose of 5) administered every 3 weeks, for a total of five cycles, completed by October 2022.

Following additional disease progression, fourth-line treatment with pembrolizumab (200 mg every three weeks) in combination with lenvatinib (20 mg daily) was initiated in November 2022. During this combination therapy, the patient developed the following adverse events: grade 3 hypertension, which required a dose reduction of lenvatinib from 20 mg to 14 mg daily; grade 2 hypothyroidism, likely attributable to pembrolizumab, managed with levothyroxine 100 µg daily; and grade 1 diarrhoea, effectively controlled with symptomatic treatment using loperamide.

In February 2023, the patient underwent a PET-CT scan, which revealed morphological stability but increased metabolic activity, suggestive of disease pseudoprogression according to the immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria (Figure 1). A follow-up evaluation in June 2023 demonstrated both morphological stability and a favourable metabolic response, allowing for the continuation of the current therapy (Figure 2).

In January 2024, the patient reported pain in the mandibular region, prompting a consultation with an

Figure 1. First PET-CT scan after beginning of pembrolizumab and lenvatinib shows morphological stability but increased metabolic activity, suggestive of disease pseudoprogression according to the iRECIST criteria. Arrow indicates hepatic nodule and its pet-scan uptake.

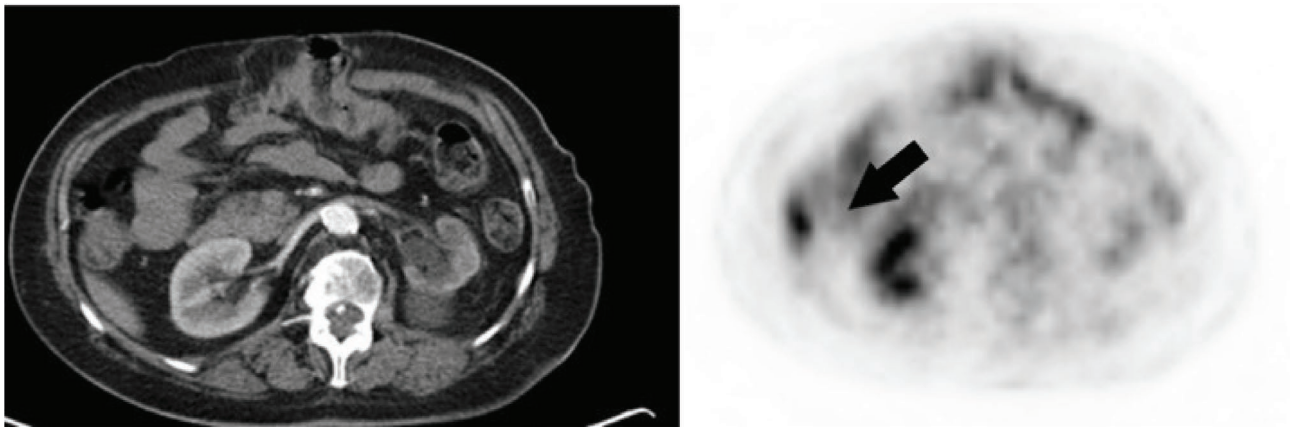
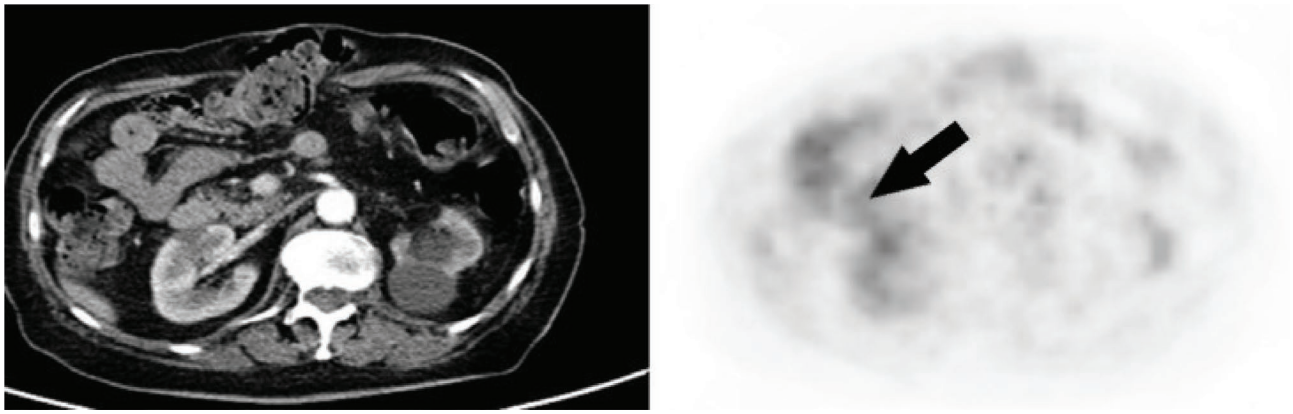


Figure 2. Second PET-CT scan after beginning of pembrolizumab and lenvatinib shows both morphological stability and a favourable metabolic response. Arrow indicates metabolic response of hepatic nodule shown in Figure 1.



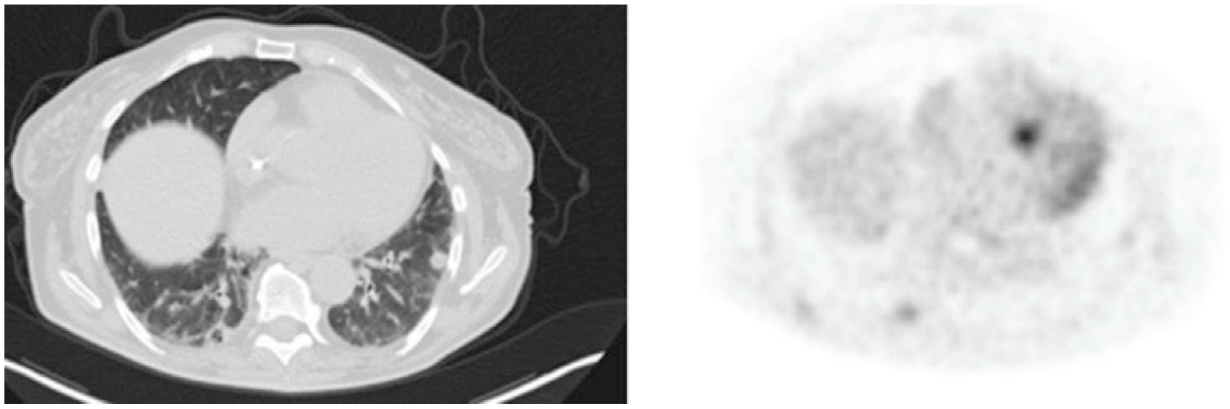
odontologist. Osteonecrosis of the jaw was diagnosed, confirmed by bone biopsy, which led to the discontinuation of denosumab.

In September 2024, a subsequent imaging evaluation revealed an increase in both the number and size of pulmonary and lymph node lesions (Figure 3). As a result, fifth-line therapy was initiated with paclitaxel (80 mg/m²) on days 1, 8 and 15 of a 28-day cycle. The patient is currently undergoing this treatment regimen.

Discussion

This case highlights the challenges of managing advanced endometrioid adenocarcinoma. Pembrolizumab, which is approved for mismatch repair-deficient or microsatellite instability-high tumours, is often combined with lenvatinib for pMMR tumours, where immunotherapy alone typically proves insufficient.[5] The adverse events observed in our patient, including hypertension and hypothyroidism, are consistent with the known toxicity profiles of these agents, necessitating dose adjustments and supportive treatments. These findings emphasize the importance of vigilant monitoring to optimize therapeutic benefit while minimizing harm.[6] Immunotherapy and targeted therapies have significantly improved survival in several cancer types, but they remain a clinical challenge. Immune-related adverse events associated with ICIs and off-target toxicities from targeted therapies require a comprehensive approach to toxicity management.[7] Early identification of at-risk patients using predictive markers, along with continuous monitoring, is essential. Advanced technologies, such as wearable health monitors and telemedicine platforms, present opportunities for proactive toxicity management. Furthermore, optimizing treatment regimens through dose adjustments or sequential scheduling can help mitigate cumulative toxicities. Achieving the balance between efficacy and tolerability requires a multidisciplinary approach, integrating oncologists, pharmacists and supportive care specialists.

Figure 3. PET-CT scan shows an increase in both the number and size of pulmonary and lymph node lesions.



In February 2023, despite metabolic progression per iRECIST, the patient exhibited morphological stability, complicating decision-making. This discordance suggests that response evaluations in immunotherapy-treated cancers require refined criteria.[8] The assessment of treatment response in immunotherapy necessitates specialized tools due to unique response patterns such as pseudoprogression and hyperprogression.[9] The iRECIST guidelines provide a standardized approach to evaluating immunotherapy outcomes by distinguishing true disease progression from transient inflammatory changes. By incorporating confirmatory scans and accounting for delayed responses, iRECIST enhances the reliability of clinical decisions in immunotherapy settings.[10] PET-CT is increasingly utilized for comprehensive disease evaluation during immunotherapy.[11] PET-CT can assess metabolic activity, offering insights into tumour biology and immune cell activity. Its ability to capture early treatment responses and differentiate viable tumour tissue from necrosis makes it a valuable adjunct to morphological criteria like iRECIST.

Conclusions

This case demonstrates the potential for long-term treatment with pembrolizumab and lenvatinib in a patient with advanced EC. It highlights the use of multimodal therapeutic strategies tailored to disease progression, patient tolerance and specific treatment goals. The observed outcomes, including manageable toxicity levels and sustained response, provide encouraging evidence for the treatment of advanced EC, even in older patients.

While a thorough risk–benefit assessment remains essential for every patient, we believe this report offers valuable insights for clinicians treating individuals with comorbidities. Furthermore, it underscores the importance of a multidisciplinary approach. Through collaboration with cardiologists and endocrinologists, we were able to select and manage the most appropriate therapy, ensuring optimal care for the patient. This integrated management model enables the tailoring of treatments, ensuring prompt support for adverse events and improving patient outcomes.

Additionally, we observed that incorporating iRECIST and PET-CT into routine clinical practice enhances the accuracy of monitoring therapeutic efficacy and disease progression. However, we acknowledge that this approach may not always be feasible in all institutions. To ensure equitable care, it is crucial to foster collaboration between smaller and larger hospitals. This partnership is essential to deliver a consistent standard of care to all patients, regardless of the size or resources of the treating institution. By sharing expertise and resources, both types of centres can provide comprehensive, high-quality care, ensuring that all patients receive optimal treatment.

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Correspondence: Amedeo Cefaliello, Department of Woman, Child and Public Health, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Largo Agostino Gemelli, 8, 00168, Rome, Italy. Email: amedeo.cefaliello@outlook.it

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