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EDITORIAL

New treatment options for advanced endometrial carcinoma Special Issue

Advancing endometrial cancer treatment: exploring immunotherapy and tyrosine kinase inhibitors through clinical cases

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Abstract

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries, with advanced-stage disease posing significant therapeutic challenges. Standard treatments, including surgery, radiotherapy and chemotherapy, have limited efficacy in recurrent or metastatic cases, necessitating novel therapeutic approaches. Recent molecular classifications of EC have identified subtypes with distinct prognostic and therapeutic implications, particularly those with high immunogenicity. Immunotherapy, specifically immune-checkpoint inhibitors targeting PD-1/PD-L1, has transformed EC treatment. The combination of pembrolizumab, an anti-PD-1 monoclonal antibody, and lenvatinib, a tyrosine kinase inhibitor (TKI), has demonstrated superior efficacy over chemotherapy in the pivotal KEYNOTE-775 trial, significantly improving progression-free and overall survival in advanced EC. Additionally, dostarlimab has shown promise as a monotherapy for mismatch repair-deficient EC, expanding treatment options. This special series in *Drugs in Context* explores these advancements through clinical case studies, highlighting real-world applications of immunotherapy and TKIs. Cases illustrate treatment responses, challenges in managing toxicities and the evolving role of molecular profiling in personalizing therapy. As research progresses, integrating immunotherapy and TKIs into routine practice is expected to improve outcomes for patients with advanced EC, offering new hope in a previously limited therapeutic landscape.

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Commentary

Endometrial cancer (EC), arising from the lining of the uterus, is the most prevalent gynaecological malignancy in developed countries and ranks as the fifth leading cause of death amongst cancer patients worldwide.[1] In Italy, approximately 8,652 new cases were estimated in 2024, accounting for 5.5% of all female cancers and representing the third most common malignancy in women aged 50–69 years.[2] Although most cases are diagnosed at an early stage and are associated with favourable outcomes, advanced and recurrent disease remains a significant clinical challenge, with markedly poor survival rates. Specifically, 5-year overall survival (OS) exceeds 80% for patients with stage I disease but drops below 17% for those diagnosed with stage IV cancer.[3]

Standard treatment strategies, including surgery, radiotherapy and chemotherapy, offer limited efficacy in advanced stages, highlighting the urgent need for innovative therapeutic approaches.[4,5] First-line chemotherapy typically comprises a platinum-based doublet regimen (carboplatin and paclitaxel) and, until recently, there were no standard second-line options following platinum failure.[6,7]

Over the past decade, molecular characterization has significantly reshaped the management of EC. Four distinct molecular subgroups have been identified based on immunohistochemistry and sequencing assays: *POLE*-mutated, mismatch repair-deficient (dMMR), p53-abnormal, and no specific molecular profile tumours.[8,9] This classification not only provides essential prognostic information but also guides therapeutic decisions as emphasized by the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines.[10]

The *POLE*-mutated and dMMR subtypes are characterized by impaired DNA repair mechanisms, resulting in high mutational burdens, increased neoantigen loads and elevated tumour-infiltrating lymphocytes. These tumours also frequently express PD-1 and its ligand PD-L1.[11] Such immunogenic features have paved the way for the use of immune-checkpoint inhibitors, which have revolutionized the management of advanced and recurrent EC.[12]

Tyrosine kinase inhibitors (TKIs) are small molecules that target various signalling pathways involved in tumour proliferation, survival and angiogenesis.[13] In addition to their antiangiogenic effects, TKIs have been shown in both preclinical and clinical studies to modulate the tumour microenvironment, shifting it from an immunosuppressive state to one that is immunostimulatory and hostile to tumour growth.[14,15] This capacity underpins the rationale for combining TKIs with immune-checkpoint inhibitors as a synergistic treatment strategy in multiple cancer types, including EC.[16]

A notable example is the combination of lenvatinib, an oral TKI, with pembrolizumab, an anti-PD-1 monoclonal antibody. This regimen leverages the anti-angiogenic effects of lenvatinib and the immune activation properties of pembrolizumab to enhance anti-tumour efficacy.[17] The pivotal Study 309/KEYNOTE-775, a multicentre, open-label, randomized, active-controlled phase III trial, evaluated the safety and efficacy of this combination in patients with advanced EC previously treated with at least one platinum-based chemotherapy regimen.[18] The study enrolled 827 patients who were randomized to receive lenvatinib plus pembrolizumab or the investigator's choice of doxorubicin or paclitaxel.[18] The combination demonstrated a median progression-free survival (PFS) of 7.2 months compared to 3.8 months with chemotherapy (HR 0.56, 95% CI 0.48–0.66; $p<0.001$). Median OS was 18.3 months *versus* 11.4 months, respectively (HR 0.62, 95% CI 0.51–0.75; $p<0.001$). Adverse events of grade ≥3 were reported in 88.9% of patients receiving lenvatinib plus pembrolizumab compared with 72.7% in the chemotherapy group.[18] In the final prespecified OS analysis, the combination maintained superior efficacy and a manageable safety profile in patients with previously treated advanced EC.[19]

Building on these findings, the ENGOT-en9/LEAP-001 trial evaluated lenvatinib plus pembrolizumab as a first-line treatment for advanced EC compared with standard chemotherapy.[20,21] Although the combination did not achieve its primary end points of PFS and OS in the overall population or the mismatch repair-proficient (pMMR) subgroup, it demonstrated significant benefits in specific subgroups. Notably, in patients dMMR tumours, the combination was associated with prolonged PFS, increased OS, a higher overall response rate (ORR) and an extended duration of response (DOR). Thus, despite not establishing superiority in the broader population, the findings underscore the relevance of biomarker-driven approaches in the treatment of EC. The favourable safety profile and quality-of-life outcomes further support the consideration of lenvatinib/pembrolizumab in selected patient populations. These results emphasize the ongoing need for personalized treatment strategies and further research to optimize first-line therapeutic options in this setting.

Another promising immunotherapeutic agent is dostarlimab, an anti-PD-1 monoclonal antibody that has shown clinical activity in patients with dMMR EC.[12] In the GARNET trial, dostarlimab monotherapy demonstrated efficacy in both dMMR/microsatellite instability-high (MSI-H) and pMMR/microsatellite stable (MSS) cohorts of patients with recurrent or advanced EC.[22] The primary end points were ORR and DOR. ORR was 43.5% (95% CI 34–53.4%) in the dMMR/MSI-H cohort, with 11 complete responses. In the pMMR/MSS cohort, ORR was 14.1% (95% CI 9.1–20.6%). Median DORs had not yet been reached at the time of analysis. Based on these results, dostarlimab was approved as monotherapy for patients with recurrent or advanced dMMR/MSI-H EC progressing after platinum-based chemotherapy.[22] Although dostarlimab has not yet been extensively combined with TKIs, its efficacy as a single agent underscores the expanding role of immunotherapy in EC treatment.[22]

The integration of TKIs and immunotherapy, particularly lenvatinib plus pembrolizumab, represents a significant advancement over the traditional carboplatin-paclitaxel doublet. This personalized approach is informed by the tumour's molecular profile and offers a dual mechanism that targets both the tumour microenvironment and the immune system. The emergence of dostarlimab further enriches the therapeutic landscape, especially for patients with dMMR tumours. Ongoing clinical trials continue to refine these strategies with the aim of optimizing outcomes and establishing their place in routine clinical practice. As research evolves, these novel treatments are expected to become standard components of the advanced EC treatment paradigm, offering renewed hope for improved patient survival and quality of life.[12]

Recognizing the importance of real-world evidence in informing clinical decision-making, we present a

series of clinical cases to illustrate and enhance the management of patients with advanced-stage EC. In brief, Fabbri et al.[23] illustrate the use of pembrolizumab and lenvatinib in a patient with advanced MSS and p53-mutated EC — subtypes associated with poor prognosis — demonstrating the real-world application of KEYNOTE-775 trial findings, with notable prolonged PFS and tolerability achieved through dose adjustments and multidisciplinary care. Lancianese et al.[24] present practical insights for clinicians by addressing the timely and relevant topic of combination immunotherapy with pembrolizumab and lenvatinib in pMMR/MSS recurrent EC. Tuninetti et al.[25] report a case of a 56-year-old woman with dMMR/MSI EC who experienced disease progression following first-line treatment with carboplatin and paclitaxel. Notably, she demonstrated a high response to subsequent immunotherapy with dostarlimab, despite initial pseudoprogression observed in one target lesion. Finally, Cefaliello et al.[26] emphasize the importance of partnerships in ensuring consistent, high-quality care for all patients, regardless of the institution's size or resources, by promoting the sharing of expertise and resources.

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