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Efficacy and safety of PD-1/PD-L1 inhibitors as immunotherapy in advanced endometrial cancer: a systematic review

Eficacia y seguridad de la inmunoterapia anti-PD-1/PD-L1 en cáncer de endometrio avanzado: una revisión sistemática

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ABSTRACT
Introduction: Endometrial cancer is the most common malignant neoplasm of the female genital tract in developed countries. The standard first-line treatment in advanced stages is platinum-based chemotherapy. However, a standardized chemotherapy regimen is not available for second and subsequent lines after disease progression. Immune checkpoint inhibitors, which target PD-1 proteins (pembrolizumab, nivolumab, dostarlimab, and sintilimab) or PD-L1 (durvalumab and avelumab), have emerged as effective alternatives in the second-line treatment of advanced or recurrent endometrial cancer, either as monotherapy or in combination with other targeted therapies. **Materials and Methods:** We conducted a bibliographic search of articles published in the last 5 years. Databases such as PubMed, Web of Science and Cochrane have been used for this purpose. **Results:** Twelve articles were selected for review that collect efficacy and safety data on the use of immunotherapy in patients with advanced endometrial cancer who have previously received at least one line of platinum-based chemotherapy treatment. Four of the publications refer to the use of pembrolizumab, in monotherapy or associated with lenvatinib, two of them being carried out by the same research team. **Conclusions:** Immunotherapy presents a high response rate in advanced endometrial cancer that expresses alteration of the DNA base repair pathway and microsatellite instability. In comparison to conventional chemotherapy in patients with advanced endometrial cancer, immunotherapy has shown efficacy, either as monotherapy or in combination with other targeted therapies.

Keywords: Endometrial cancer, immunotherapy, targeted therapy, immune checkpoint inhibitors.

RESUMEN
Introducción: El cáncer de endometrio es la neoplasia maligna más frecuente del tracto genital femenino en países desarrollados. El tratamiento estándar de primera línea en estadios avanzados es la quimioterapia basada en platino. Sin embargo, no se dispone de un régimen estándar de segunda línea y sucesivas tras la progresión de la enfermedad. Los inhibidores de punto de control inmunológico, que actúan contra las proteínas PD-1 (pembrolizumab, nivolumab, dostarlimab y sintilimab) o PD-L1 (durvalumab y avelumab), en monoterapia o en combinación con otras terapias dirigidas, han surgido como alternativas eficaces en el tratamiento de segunda línea del cáncer de endometrio avanzado. **Material y métodos:** Se realizó una búsqueda bibliográfica de artículos publicados en los últimos cinco años en las bases de datos PubMed, Web of Science y Cochrane. **Resultados:** Se seleccionaron 12 artículos para su revisión; estos recogen datos de la eficacia y la seguridad del uso de inmunoterapia en pacientes con cáncer de endometrio avanzado que ya habían recibido al menos una línea de quimioterapia basada en platino. Cuatro de las publicaciones se refieren al empleo de

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pembrolizumab, en monoterapia o en combinación con lenvatinib, y dos de ellas fueron realizadas por el mismo equipo de investigación. **Conclusiones:** La inmunoterapia presenta una elevada tasa de respuesta en el cáncer de endometrio avanzado que expresa alteraciones de la vía reparadora del ADN e inestabilidad de microsatélites. Ha demostrado además eficacia respecto a la quimioterapia convencional, tanto en monoterapia como en combinación con otras terapias dirigidas, en pacientes con cáncer de endometrio avanzado.

Palabras Clave: neoplasias endometriales, inmunoterapia, terapia dirigida, inhibidores de puntos de control inmunitarios.

1. Introduction

Endometrial cancer (EC) is the most frequent malignant neoplasm of the female genital tract in developed countries [1], affecting mainly women over 50 years of age, with a median age at diagnosis of 63 years old [2,3]. Its incidence has increased due to population aging and obesity [1-5]. Although more than 90% of cases are sporadic, up to 10% are hereditary in origin, generally associated with Lynch syndrome [6].

Microsatellite instability (MSI) is a common genetic abnormality in EC caused by defects in proteins of the DNA repair mechanism (mismatch repair, MMR). Depending on the degree of alteration, MSI can be high (MSI-H) or low (MSI-L) [7]. About 30% of ECs are deficient in MMR (dMMR) and MSI-H proteins, while most of them are tumors with microsatellite stability (MSS) and presence of MMR (pMMR) [8,9].

Twenty percent of patients with SC are diagnosed with advanced or metastatic disease (stage III or IV). Between 10-15% of ECs recur and 80-90% of recurrences occur within the first three years after diagnosis [9]. The standard first-line treatment of advanced or recurrent unresectable SC is platinum-based chemotherapy (QT) using the combination of carboplatin and paclitaxel [10,11]. Considering that second-line treatment options are limited, and advanced or recurrent EC ends up being largely resistant to QT, it is crucial to develop more effective and safer novel therapies [12,13].

PD-1 and PD-L1 proteins negatively regulate T-cell activity, preventing tumor cell killing and favoring cancer progression [14]. Immune checkpoint inhibitors (ICIs) block this interaction and have demonstrated antitumor activity with a good safety profile in patients previously treated with QT [12,13].

Monoclonal antibodies directed against PD-1 or PD-L1 enhance the immune response to attack cancer cells [12]. Their efficacy can be enhanced when combined with targeted therapies, such as receptor tyrosine kinase (RTK) inhibitors (e.g., Lenvatinib) or poly (ADP-ribose) polymerase enzyme inhibitors (PARP, e.g., Olaparib).

2. Materials and Methods

2.1 Primary objective

To evaluate the efficacy and safety of PD-1/PD-L1 inhibitors therapy, in monotherapy or in combination, in advanced SC.

2.2 Secondary objectives

To study the efficacy of immunotherapy and targeted therapies in patients with advanced CE dMMR/MSI-H versus pMMR/MSS.

To analyze the efficacy and safety of immunotherapy and targeted therapies versus QT in second-line treatment in patients with advanced SC.

2.3 Study design

A descriptive, observational, systematic review with a qualitative approach was carried out.

2.4 Databases and Search Terminology

The bibliographic search was performed in the PubMed, Web of Science, and Cochrane databases.

The search strategy was conducted by combining the MeSH terms "immune checkpoint inhibitors", "Pembrolizumab", "dostarlimab", "Lenvatinib", "paclitaxel", "carboplatin", "doxorubicin" and "endometrial neoplasms" with the Boolean operators AND and OR, as follows: (((((((((Immune Checkpoint Inhibitors)) OR (Pembrolizumab)) OR (Dostarlimab)) OR (Lenvatinib)) OR (Paclitaxel)) OR (Carboplatin)) OR (Doxorubicin)) AND (Endometrial Neoplasms))).

2.5 Inclusion criteria

Randomized and non-randomized clinical trials published in the last 5 years, in English and in humans, with patients who received at least one line of platinum-based QT.

2.6 Exclusion criteria

Studies that addressed several solid tumors (e.g., EC and ovarian cancer), compared brachytherapy and/or radiotherapy versus pharmacological treatments, evaluated the efficacy of the combination of immunotherapy and QT versus QT in monotherapy, or were cost-effective studies.

2.7 Study variables

The clinical variables evaluated in the studies were objective response rate (ORR), overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), disease progression (DP), duration of response (DR), and disease control rate (DCR) [15]. RECIST 1.1 and iRECIST criteria were applied [15,16]. Safety and toxicity were evaluated according to CTCAE v4 criteria [17], including the most frequent and serious adverse events (AEs).

2.8 Selection of articles

Twelve studies evaluating the effectiveness and toxicity of PD-1/PD-L1 inhibitor agents and targeted therapies in advanced SC were selected. The selection from electronic databases was performed by title and abstract, followed by a full-text review, choosing those that met the inclusion criteria. Figure 1 presents the article selection process using a PRISMA flowchart [18].

3. Results and Discussions

Table 1 lists the characteristics of the 12 studies [19-30]. In all of them, patients presented advanced or recurrent SC.

Five studies evaluated PD-1/PD-L1 inhibitors agents in monotherapy, including Durvalumab [20], Pembrolizumab [23,26,27], and Dostarlimab [28], in addition to a study on Cabozantinib [19]. Six analyzed combinations of PD-1/PD-L1 inhibitors and targeted therapies, including Nivolumab-Cabozantinib [21], Sintilimab-Antolinib [22], Avelumab-Talazoparib [24], Durvalumab-Olaparib [25], and Pembrolizumab-Lenvatinib [29,30]. Except for the study by Wei et al [22], all were multicenter.

3.1 Efficacy of immunotherapy and targeted therapies in patients with advanced or recurrent dMMR/MSI-H vs. pMMR/MSSS SC.

Studies highlight the differential efficacy of immunotherapy according to the molecular profile of EC, especially between dMMR/MSI-H and pMMR/MSS subtypes. PD-1/PD-L1 inhibitor agents, such as

Pembrolizumab [23,26], Durvalumab [20] and Dostarlimab [27] show higher antitumor activity in dMMR/MSI-H ECs, with ORR between 43.5% and 58%, due to their high neoantigen load and higher PD-1/PD-L1 expression [31]. Factors such as tumor microenvironment and previous exposure to QT also influence the response, as QT can increase tumor antigen presentation and immune susceptibility [20].

The combination of immunotherapy with antiangiogenic agents has been shown to extend efficacy in molecular subtypes less sensitive to ICI monotherapy. In the KEYNOTE-146 study, Pembrolizumab and Lenvatinib achieved an ORR of 39.8% and a PFS of 7.4 months, even in pMMR ECs [29]. Sintilimab and Anlotinib achieved an ORR of 100% in dMMR/MSI-H and 85.7% in pMMR, although the sample size limits the generalizability of the results [22].

Combinations of ICIs with PARP inhibitors have also been investigated, especially in patients with pMMR CE, although the results are less conclusive [24,25].

In general, treatments were well tolerated, with mild AEs including fatigue, diarrhea, anemia, and hypothyroidism [20,26,27]. Less frequent severe AEs include hypertension, neutropenia, and elevated liver enzymes [29]. Combinations with antiangiogenic agents showed higher rates of grade ≥3 AEs, such as hypertension and lipase elevation, but were manageable [22,29].

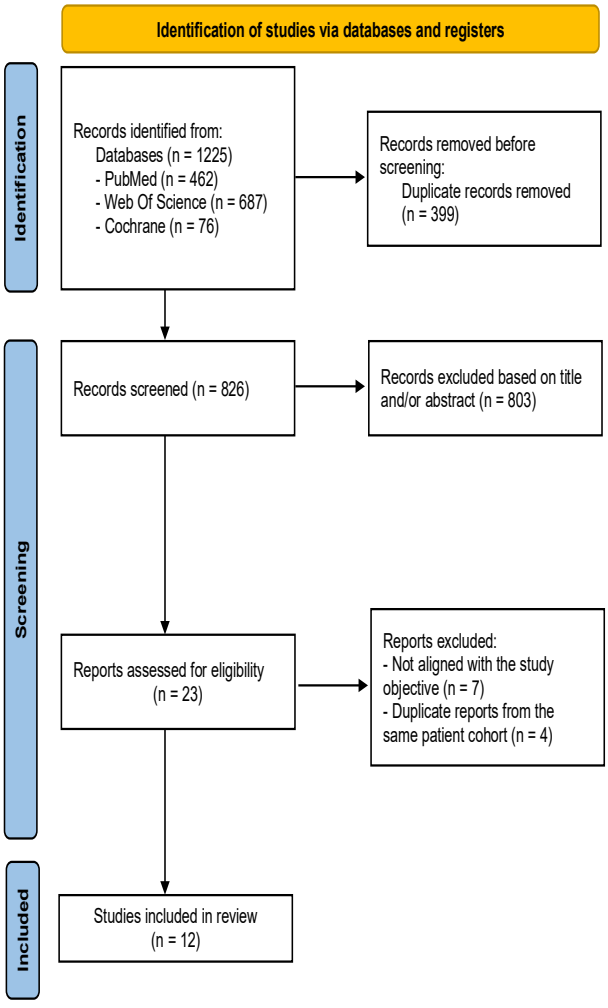

Figure 1 . Flow chart according to the PRISMA model of item selection. Source: Own elaboration based on the PRISMA 2020 flow chart.

Table 1. Description of the main characteristics and results of the studies.

Study data	n	Target	Conclusions
Dhani et al. (2020) [19]. United States.	102	Phase II trial on the efficacy of Cabozantinib in monotherapy in 2 cohorts of patients. Primary endpoint: PFS at 12 weeks and ORR.	Cabozantinib showed activity in the experimental cohort (endometrioid and serous histology), with a median PFS of 4.6 months and 6-month PFS of 37%. In the exploratory cohort (other histologies), PFS at 12 weeks was 47% and ORR 16%. Most common AEs: fatigue (61%), diarrhea (51%), palmar-plantar erythrodysesthesia (39%), and hypertension (25%).
Antill et al. (2021) [20]. Australia.	71	PHAEDRA phase II trial on the efficacy of Durvalumab in monotherapy: CE dMMR (n=35) and CE pMMR (n=36). Primary objective: TRO	Durvalumab showed ORR of 47% in dMMR EC compared with 3% in pMMR EC. OS at 12 months was 71% in dMMR and 51% in pMMR. The most frequent AEs were related to immunotherapy (20%).
Lheureux et al. (2022) [21]. United States.	54	Phase II trial on the efficacy of Cabozantinib and Nivolumab (n=36) versus Nivolumab monotherapy (n=18). Primary target: SLP.	The combination of Cabozantinib and Nivolumab significantly improved PFS compared to Nivolumab monotherapy (5.3 months vs. 1.9 months). Most frequent AEs: diarrhea (42%), AST elevation (42%), fatigue (36%) and anorexia (31%).
Wei et al. (2022) [22]. China.	23	Phase II trial on the efficacy of the combination of Sintilimab and Anlotinib in dMMR/MSI-H (n=9) and pMMR/MSS (n=14) ECs. Primary objective: TRO.	The combination obtained an ORR of 73.9%, reaching 100% in dMMR/MSI-H EC and 85.7% in pMMR/MSS EC. A total of 43.5% presented adverse effects, the most common being palmo-plantar erythrodysesthesia (100%), skin rash (69.6%), and hypothyroidism (69.6%).
Bellone et al. (2022) [23]. United States.	24	Phase II trial on the efficacy of Pembrolizumab in monotherapy in patients with CE dMMR/MSI-H (75% sporadic, 25% hereditary, associated with Lynch syndrome). Primary objective: TRO.	Pembrolizumab showed antitumor activity in recurrent dMMR/MSI-H SC. ORT, PFS and OS results were superior in patients with EC associated with Lynch syndrome. Most common AEs: diarrhea (12.4%), skin disorders (7.9%), fatigue (6.8%), and perfusion-related reactions (5.6%).
Konstantinopoulos et al. (2022) [24]. United States.	35	Phase II trial on the efficacy and safety of Avelumab and Talazoparib in pMMR SC. Primary objective: ORT and PFS at 6 months. .	The combination demonstrated a favorable AE profile and met the prespecified criteria for further evaluation in pMMR CE. ORR was 11.4% and PFS at 6 months was 22.9%. The most common grade 3-4 AEs: anemia (46%), thrombocytopenia (29%), and neutropenia (11%).
Post et al. (2022) [25]. Netherlands.	50	DOMEC trial (phase II) on the efficacy of the combination Durvalumab plus Olaparib. Primary endpoint: PFS at 6 months (effective treatment if PFS rate at 6 months at ≥ 50%).	The combination was well tolerated, but did not achieve the target PFS ≥ 50%, so it was not advanced to phase III. Median PFS was 3.4 months, and median OS was 8.4 months. In CE dMMR, median PFS was 5.7 months and ORR was 16%. Most frequent AE's: fatigue (44%), nausea (38%), anemia (32%), and diarrhea (26%).

O'Malley et al. (2022) [26]. United States.	90	KEYNOTE-158 trial (phase II) on the efficacy and safety of Pembrolizumab in monotherapy in dMMR/MSI-H SC. Primary objective: TRO	Pembrolizumab showed durable antitumor activity in previously treated dMMR/MSI-HSC. ORR was 48% and median PFS was 13.1 months. Median OS was not reached. Most AEs were grade 1-2 (76%), the most frequent being pruritus (24%), fatigue (21%), and diarrhea (16%).
Study data	**n**	**Target**	**Conclusions**
Oaknin et al. (2022) [27]. United States.	264	GARNET trial (phase I) on the efficacy and safety of dostarlimab: CE dMMR/MSI-H (n=108) and CE pMMR/MSS (n=156). Primary target: TRO and DR.	Dostarlimab showed antitumor activity in dMMR/MSI-HSCs, with an ORR of 43.5%, being less effective in pMMR/MSSSCs (ORR of 14.1%). Grade 1-2 AEs: fatigue (17.6%), diarrhea (13.8%), and nausea (13.8%).
Mathews et al. (2022) [28]. United States.	325	Indirect comparison of the efficacy and safety of Dostarlimab (GARNET trial) in CE dMMR/MSI-H (n=92) vs. Doxorubicin (ZoptEC trial; n=233). Primary objective: to compare OS.	Dostarlimab showed greater OS than Doxorubicin, with a 59% lower risk of death. PFS was 2.5 times longer (12.2 vs. 4.9 months), as was ORR (44% vs. 14%). AEs were similar in both treatments, with fewer serious AEs in Dostarlimab (34.1% vs. 30.1%).
Makker e t al. (2023) [29]*. United States.	108	Trial 111/KEYNOTE-146 (phase Ib/II), on the long-term efficacy and safety of Pembrolizumab and Lenvatinib. Primary objective: TRO.	The combination of Pembrolizumab and Lenvatinib showed ORR of 39.8% and median RD of 22.9 months. Median PFS was 7.4 months and OS was 17.7 months. Most frequent AEs: hypertension (33.3%), lipase elevation (9.3%), fatigue (8.3%) and diarrhea (7.4%).
Makker et al. (2023) [30]**. United States.	827	309/KEYNOTE-775 trial (phase III) on the efficacy and safety of Pembrolizumab and Lenvatinib (n=411) vs. QT (doxorubicin and paclitaxel; n=416). Primary target: SG and SLP.	Pembrolizumab plus Lenvatinib was more effective than QT, with an OS of 18.7 months vs. 11.9 months and a median PFS of 7.3 months vs. 3.8 months. ORR was higher in Pembrolizumab + Lenvatinib (32.4%) than in QT (15.1%), achieving CR in 5.8% vs. 2.6%. Most common AEs: hypertension (65%) in the Pembrolizumab and Lenvatinib arm; and anemia (48.7%) in the QT arm.

*This article is an update of Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol*(.) (2020;38(26):2981-92. **This article is an update of:) Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. (Lenvatinib Plus Pembrolizumab for Advanced Endometrial Cancer.) *N Engl J Med*(. 2022;386(5):437-48. (ORR: objective response rate; PFS: progression-free survival; AE: adverse events; EC: endometrial cancer; DR: duration of response; OS: overall survival; QT: chemotherapy; CR: complete response).

3.2 Efficacy and safety of immunotherapy and targeted therapies against QT in second line of treatment in patients with advanced or recurrent SC.

The reviewed studies show that immunotherapy and targeted combinations have shown greater efficacy than conventional QT in patients with advanced or recurrent SC, especially in terms of survival and disease control in both pMMR and dMMR tumors.

In the study by Dhani et al [19], Cabozantinib showed improved disease control rates and manageable toxicity, although AEs such as gastrointestinal fistulas were reported, especially in patients with carcinosarcomas. Pseudoprogression, a phenomenon of ICIs, involves an initial increase in tumor burden followed by regression [32]. According to Lheureux et al [21], the combination of Cabozantinib and Nivolumab showed promising synergy between both mechanisms of action, outperforming monotherapy with ICIs and standing out as a potential strategy in immunotherapy-resistant EC.

Dostarlimab showed superiority over QT (Doxorubicin), with lower toxicity and better safety profile [28]. However, its indirect comparison with Doxorubicin implies possible methodological biases as it was not performed in a randomized controlled trial. The KEYNOTE-775 trial highlighted the significant benefit of Pembrolizumab and Lenvatinib in terms of OS and PFS. Although toxicity was high, proper management of AEs optimizes their therapeutic benefit [30].

4. Conclusions

Immunotherapy, both in monotherapy and in combination, has shown greater efficacy in patients with dMMR/MSI-H SC than in pMMR/MSS SC. PD-1/PD-L1 inhibitor agents have achieved superior response rates in dMMR/MSI-H tumors due to their high neoantigen load, increased lymphocyte infiltration and PD-1/PD-L1 overexpression, making DNA repair deficiency a key predictive marker. However, the resistance observed in some dMMR/MSI-H tumors suggests the need for future research to identify responsible mechanisms, such as alterations in the tumor microenvironment, changes in antigen presentation or even additional mutations in genes involved in the immune response.

Pembrolizumab, in monotherapy or combined with Lenvatinib, has demonstrated superiority over conventional QT (Doxorubicin or Paclitaxel) in terms of PFS, OS, and ORR, consolidating its position as a standard option for second-line treatment. Although hypertension is the most common AE, its safety profile is manageable. For its part, Dostarlimab, evaluated in the GARNET trial, has shown a favorable balance between efficacy and safety, especially in patients with dMMR/MSI-H SC. However, future comparative and randomized studies are needed to better define its role in the treatment of advanced SC.

5. Abreviations

ADP-ribose: polypeptide enzyme inhibitors

CE: endometrial cancer

dMMR: MMR protein deficiency

DR: duration of response

AE: adverse events

ICIs: immune checkpoint inhibitors

TKI: receptor tyrosine kinase inhibitors

MMR: DNA mismatch repair mechanism

MSI: microsatellite instability

MSI-H: microsatellite instability-high

MSI-L: microsatellite instability-low

MSS: microsatellite stability

PARP: polymerase chain reaction

pMMR: presence of MMR

PR: disease progression

CT: chemotherapy

CR: complete response

PR: partial response

OS: overall survival

PFS: progression-free survival

TBI: disease control rate

ORR: objective response rate

6. Administrative Information

6.1 Contributions of the Authors

1. Conceptualization: Silvia Vázquez Gómez.
2. Formal analysis: Silvia Vázquez Gómez, Alba Díaz Fernández.
3. Research: Silvia Vázquez Gómez, Alba Díaz Fernández.
4. Methodology: Silvia Vázquez Gómez.
5. Project administration: Silvia Vázquez Gómez.
6. Supervision: Silvia Vázquez Gómez, Alba Díaz Fernández.
7. Validation: Silvia Vázquez Gómez, Alba Díaz Fernández.
8. Visualization: Silvia Vázquez Gómez, Alba Díaz Fernández.
9. Editor - original draft: Silvia Vázquez Gómez.
10. Writing - proofreading and editing: Silvia Vázquez Gómez, Alba Díaz Fernández.

All authors read and approved the final version of the manuscript.

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6.3 Data and material Availability

Data is available upon request to the corresponding author. No other materials are reported.

7. Declarations

The authors declare that the information presented in this manuscript has been obtained and analyzed in an ethical and rigorous manner. However, results and conclusions presented are the sole responsibility of the authors and do not necessarily reflect the opinion of the journal or its editors. The journal and the editors shall not be liable for misuse or misinterpretation of the content of the article.

In addition, authors release the journal from liability for any unintentional errors, omissions, or consequences arising from the publication of this manuscript. Authors assume responsibility for the originality of the work and for possible ethical or legal conflicts.

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