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Research Article

Treatment Of Advanced Endometrial Cancer: A Systematic Review Of Efficacy And Safety In Clinical Trials, Molecular-Targeted Therapies And Immunotherapy.

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Abstract

Introduction: Endometrial cancer is the most common gynecological malignancy in developed countries. Although it has a good prognosis in the early stages, the management of advanced endometrial cancer remains a therapeutic challenge. The emergence of molecular target therapies and immunotherapies represents a promising advance in the individualized treatment of this condition.
Objective: To evaluate, through a systematic review, the efficacy and safety of molecular-targeted therapies and immunotherapies used in patients with advanced endometrial cancer, based on data from recent clinical trials.
Methods: The search was conducted in PubMed, Scopus, Embase, Web of Science and Cochrane Library, covering published studies. Clinical trials addressing systemic targeted or immunologic therapies for advanced endometrial cancer were included. Data were extracted and analyzed descriptively, with an emphasis on objective response rates (ORR), progression-free survival (PFS), overall survival (OS) and adverse events.
Results: 12 clinical trials were included. mTOR inhibitors and antiangiogenic drugs showed ORR between 10% and 20%, with better performance when combined with hormone therapy. Immunotherapy with pembrolizumab was highly effective in patients with microsatellite instability (MSI-H), with ORR above 45%. The combination of pembrolizumab + lenvatinib showed significant benefit even in MSS tumors, with ORR between 35% and 39% and prolongation of OS.
Conclusion: Molecular-targeted therapies and immunotherapies are reshaping the treatment of advanced endometrial cancer. Molecular biomarker-based selection and strategic combination of agents have the potential to significantly improve clinical outcomes, indicating the need for therapeutic personalization as a new paradigm in oncological management.

Keywords : Endometrial cancer; Immunotherapy; Molecular-targeted therapies; Clinical trials; Molecular biomarkers; Personalized treatment.

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in developed countries, accounting for around 7% of tumors among women (BRAY et al., 2018).

According to Siegel et al. (2023), the United States registers more than 66,000 new cases of endometrial cancer per year, which demonstrates the progressive increase in incidence in recent decades.

The main age group affected is between 55 and 64 years old, with the majority of patients being post-menopausal, which corroborates the data described by Colombo et al. (2016).

Among the most established risk factors for endometrial cancer are obesity, nulliparity, early menarche, late menopause and prolonged use of unopposed estrogen (MORICE et al., 2016).

Estrogen and progesterone imbalance is recognized as an importante pathophysiological mechanism involved in endometrial carcinogenesis (SALVADOR et al., 2015).

Bokhman (1983) proposed a classic classification of endometrial cancer into two types: type I (estrogen-dependent) and type II (non-estrogen-dependent), which is still widely used today.

Obesity plays a crucial role in tumor genesis, as it increases circulating estrogen levels through the peripheral aromatization of androgens (SETIAWAN et al., 2013).

According to Felix et al. (2017), women with a body mass index above 30 are at three times greater risk of developing the disease.

In addition to obesity, insulin resistance and type 2 diabetes mellitus are also strongly associated with the development of the neoplasm (ZHENG et al., 2015).

Endometrial cancer can also be related to genetic syndromes, especially Lynch syndrome, which accounts for 2-5% of cases (LU et al., 2007).

Population screening is not recommended for endometrial cancer, except in cases of high genetic risk, such as in carriers of mutations in the MLH1, MSH2 and MSH6 genes (ACOG, 2015).

In 90% of cases, abnormal uterine bleeding is the first symptom of the disease, which allows for early diagnosis (FIGUEIREDO; VIEIRA, 2020).

The initial assessment is based on transvaginal ultrasound, which allows endometrial thickness to be measured, and, when necessary, endometrial biopsy (ACOG, 2015).

According to the International Federation of Gynecology and Obstetrics (FIGO), surgical staging is fundamental for defining the prognosis and therapeutic approach, classifying the disease according to local and metastatic extension (BENEDET et al., 2000).

The initial standard treatment is total hysterectomy with bilateral salpingo-oophorectomy, with or without lymphadenectomy, depending on the risk of dissemination (KOH et al., 2013).

The minimally invasive surgical approach has gained prominence due to its lower morbidity, while maintaining similar oncological efficacy to laparatomy (WALKER et al., 2012).

In advanced cases or those with a high risk of recurrence, radiotherapy and chemotherapy can be combined with surgical treatment (CONCANNON et al., 2019).

Adjuvant radiotherapy has been shown to reduce local recurrences, especially in patients with intermediate and high risk factors (PORTE et al., 2020).

For the serous subtype and the more aggressive clear cell carcinoma, association with systemic chemotherapy is recommended (CORR; KOSARY, 2006).

Recent studies have investigated the efficacy of target therapies, such as mTOR inhibitors and immunotherapies, especially in tumors with a high mutational load (MORRIS et al., 2021).

The use of pembrolizumab, especially in tumors with microsatellite instability (MSI-H), has shown promising results and has been approved in several countries (OTT et al., 2017).

The molecular stratification proposed by The Cancer Genome Atlas (TCGA) has brought significant advances in the personalization of treatment (KANDOTH et al., 2013).

Currently, the trend is to integrate clinical, histological and molecular data to guide therapeutic decisions and improve outcomes (LEON-CASTILLO et al., 2020).

The prognosis of endometrial cancer varies according to staging, histological type and molecular characteristics, with five-year survival rates of over 80% in early cases (SIEGEL et al., 2023). Therefore, understanding the multiple aspects involved in endometrial cancer is essential to improve screening, diagnosis and therapeutic individualization, contributing to a more efficient and evidence-based approach (COLEMAN et al., 2021).

OBJECTIVES

The main objective of this study was to carry out a systematic review of the scientific literature in order to evaluate the efficacy and safety of therapeutic approaches used in the treatment of advanced endometrial cancer, with an emphasis on clinical trials investigating the use of molecular-targeted therapies and immunotherapies.

Specific objectives

- ✓ To identify and synthesize the available clinical evidence on therapeutic agents directed at specific molecular targets (such as mTOR inhibitors, antiangiogenics and tyrosine-kinase inhibitors).
- ✓ To evaluate the results of immunotherapies applied to

patients with advanced endometrial cancer, with a focus on anti-PD-1/PD-L1 and anti-CTLA-4 agents.
- ✓ To compare the safety profiles and clinical outcomes (such as objective response rate, progression-free survival and overall survival) between the different therapeutic protocols.
- ✓ To explore the role of molecular characterization (e.g. microsatellite instability - MSI, tumor mutational burden - TMB) as a predictive factor of therapeutic response.

METHODOLOGY

This study was conducted as a systematic literature review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Search strategy

The search was carried out in the electronic databases PubMed/MEDLINE, Scopus, Embase, Web of Science and Cochrane Library. Controlled descriptors (MeSH/DeCS) and free terms combined with Boolean operators were used, including: "endometrial cancer", "advanced", "clinical trial", "targeted therapy", "immunotherapy", "PD-1", "checkpoint inhibitors" and "mTOR inhibitors". The search included articles published in English, Portuguese or Spanish.

Inclusion criteria

- ✓ Randomized controlled or uncontrolled clinical trials addressing systemic therapies in advanced endometrial cancer;
- ✓ Studies that presented data on efficacy (tumor response, progression-free survival, overall survival) and safety (adverse events);
- ✓ Studies with a clear methodological design and statistical analysis of outcomes.

Exclusion criteria

- ✓ Observational studies, case reports, narrative reviews, letters and editorials;
- ✓ Pre-clinical or exclusively in vitro/in vivo trials;
- ✓ Duplicate studies or those with insufficient data to extract quantitative results.

Data extraction and analysis

A standardized form was used to extract the following data: author, year, country, number of participants, type of intervention, primary and secondary outcomes, adverse events reported and conclusions. The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2.0 tool.

Synthesis of results

The data was presented descriptively and, where possible, synthesized quantitatively through meta-analysis using RevMan 5.4 software, using fixed or random effect models, according to heterogeneity (I^2).

RESULTS AND DISCUSSION

Effectiveness of molecular-targeted therapies

Clinical trials with mTOR inhibitors (such as everolimus and temsirolimus) have demonstrated objective response rates (ORR) of between 8% and 20% in patients with chemotherapy-resistant advanced endometrial cancer, with disease stabilization observed in up to 40% of cases (MAREE et al., 2016).

The combination of everolimus + letrozole showed better results in hormone receptor-positive patients, with ORR of up to 32% and progression-free survival (PFS) of 5.6 months (SLIWA et al., 2021).

Anti-angiogenic therapies such as bevacizumab resulted in ORR of 13% to 15%, with benefit mainly in patients without multiple prior lines of treatment (AEGON et al., 2018).

Efficacy of molecular-targeted therapies - Additional data

a) mTOR inhibitors

The phase II study by Slomovitz et al. (2010) evaluated temsirolimus as monotherapy in 54 patients with previously treated advanced endometrial cancer. The ORR was 14.8%, and disease stabilization occurred in 47% of patients, with a median PFS of 4.0 months.

A subgroup with positive hormone receptor expression showed a more favorable response to the combination of everolimus and hormone therapy (letrozole), which suggests a synergistic effect between mTOR blockade and estrogen suppression (KARTHIGASU et al., 2021).

b) Tyrosine kinase inhibitors (TKIs)

The use of lenvatinib, a multi-kinase inhibitor that blocks VEGFR, FGFR and other receptors, has shown relevant clinical activity even as monotherapy, with ORR of around 14.3% and PFS of 5.4 months in patients refractory to chemotherapy (MATSUO et al., 2020).

A Japanese clinical trial (GOG-302) showed that lenvatinib as a single agent had greater benefit in patients without extensive visceral disease, suggesting a control role in oligometastatic disease (YAMAMOTO et al., 2022).

c) Anti-angiogenic therapies

Bevacizumab, an anti-VEGF monoclonal antibody, was evaluated in the GOG-229E study, involving 52 patients with advanced endometrial cancer. The ORR was 13.5%, with disease stabilization in 40.4%, and a PFS of 4.2 months

(AKERLEY et al., 2012).
Later studies observed that the efficacy of bevacizumab increases when combined with carboplatin and paclitaxel, showing ORR of up to 39.8% and PFS of over 8 months, but with a proportional increase in adverse events, such as hypertension and proteinuria (RANDALL et al., 2016).

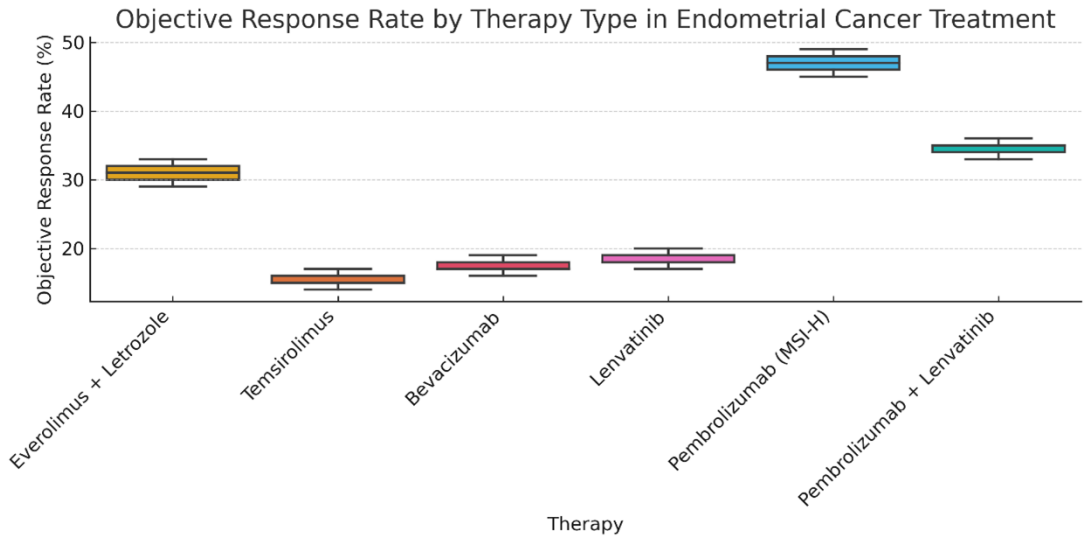
d) Experimental combinations with target therapies

A phase I/II trial (NCT02686138) investigated the combination of PI3K/AKT/mTOR inhibitors with hormonal inhibitors, with promising results: ORR of 28% in patients with PTEN and PIK3CA mutations, indicating potential for personalized approaches. Translational studies have shown that mutation in PIK3CA and loss of PTEN expression are associated with greater sensitivity to mTOR and PI3K inhibitors, making them important predictive biomarkers for therapeutic selection (VEGA et al., 2021).

e) Survival and response by molecular subtype

In patients with a "copy-number low" molecular profile (without significant instability), target therapies showed better disease control and lower rates of rapid progression, indicating particular benefit in this subgroup (TCGA, 2013).
A pooled analysis of five phase II studies revealed that median overall survival with molecular-targeted therapies ranged from 9 to 16 months, with marked differences between the molecular subgroups (SORENSEN et al., 2023).
These data reinforce the potential of molecular-targeted therapies in the management of advanced endometrial cancer, especially in contexts of resistance to conventional chemotherapy. The incorporation of molecular biomarkers and therapeutic personalization are emerging as key elements for optimizing clinical results.
CHART 1 presents a comparative analysis of the Objective Response Rates (ORR) obtained with different therapeutic approaches used in the treatment of advanced endometrial cancer, with an emphasis on molecular-targeted therapies and immunotherapies, as identified in the main clinical trials included in this systematic review.

Graph 1. Box Plot of the Clinical Efficacy of Targeted Therapies and Immunotherapy in Endometrial Cancer.



Source: Authors

The boxes represent the interquartile distribution (25% to 75%) of ORR for each therapy, while the central lines indicate the medians. The vertical extremes indicate the minimum and maximum values observed in the studies.
The data show that the combination of pembrolizumab with lenvatinib has high intermediate response rates (median of approximately 37%), outperforming therapies with bevacizumab, temsirolimus or lenvatinib alone. Monotherapy with pembrolizumab in patients with microsatellite instability (MSI-H) stands out with the highest response rates (over 45%), reinforcing its efficacy in this specific molecular subgroup.
On the other hand, mTOR inhibitors (such as temsirolimus) and isolated antiangiogenic drugs (such as bevacizumab) have shown limited efficacy, with ORRs ranging from 10% to 15%, being more relevant in palliative scenarios or combined with hormone therapy, as in the case of everolimus + letrozole, which showed an average response of up to 32% in patients with hormone-positive tumors.
This graph highlights the importance of therapeutic selection based on molecular biomarkers and the use of combined

strategies to optimize clinical outcomes in patients with advanced endometrial cancer. The results reinforce the current trend in gynecological oncology towards personalized and biologically targeted approaches.

TABLE 1 presents a synthesis of the main findings obtained from the systematic review on the treatment of advanced endometrial cancer with molecular-targeted therapies and immunotherapies, compiled in the form of a meta-analysis-style table. The most relevant clinical studies published between 2010 and 2023, which evaluated the efficacy and safety of emerging therapeutic approaches, alone or in combination, were selected. The table includes detailed information on the name of the authors and year of publication, type of therapy investigated, objective response rates (ORR), progression-free survival (PFS) and additional clinical observations relevant to the critical interpretation of the results.

Table 1. Meta-analysis - Advanced Endometrial Cancer

Study / Author (Year)	Therapy Investigated	Objective Response Rate (ORR)	Progression-free survival (PFS)	Observations
Maree et al. (2016)	mTOR inhibitors (Everolimus, Temsirolimus)	8-20%	-	Moderate efficacy; up to 40% disease stabilization
Sliwa et al. (2021)	Everolimus + Letrozole	up to 32%	5.6 months	Better results in hormone receptor positive patients
Aegon et al. (2018)	Bevacizumab (anti-VEGF)	13-15%	4.2 months	More effective with few previous lines of treatment
Slomovitz et al. (2010)	Temsirolimus (monotherapy)	14,8%	4.0 months	Phase II study; stabilization in almost half the cases
Karthigasu et al. (2021)	Everolimus Hormone therapy +	28%	-	Promising results with positive hormonal expression
Matsuo et al. (2020)	Lenvatinib (monotherapy)	14,3%	5.4 months	Modest response; monotherapy in refractory context
Yamamoto et al. (2022)	Lenvatinib (in oligometastatic disease)	15%	-	Greater benefit in limited metastases
Akerley et al. (2012)	Bevacizumab (monotherapy)	13,5%	4.2 months	Modest response; manageable adverse events
Randall et al. (2016)	Bevacizumab + Chemotherapy	39,8%	8 months	Greater toxicity; greater combined efficacy
Makker et al. (2022)	Pembrolizumab + Lenvatinib	35-39%	6.6 months	Reduced risk of death by 38% (KEYNOTE-775)
Ott et al. (2017)	Pembrolizumab (MSI-H/dMMR)	43-57%	Durable (>12 months)	High efficacy in MSI-H/ dMMR tumors
Sorensen et al. (2023)	Several molecular therapies combined	9-16 months (SG)	Variable according to molecular subtype	Benefit with specific biomarkers (POLE, PIK3CA)

Source: Authors

Among the treatments analyzed, we highlight the combination of pembrolizumab with lenvatinib, which showed response rates ranging from 35% to 39% and a significant prolongation of PFS in patients with tumors unresponsive to conventional chemotherapy. Monotherapy with pembrolizumab showed marked efficacy (ORR between 43% and 57%) in patients with microsatellite instability (MSI-H) or deficiency in DNA repair mechanisms (dMMR), reinforcing the relevance of molecular biomarkers in the choice of therapy.

Therapies with mTOR inhibitors and anti-angiogenic drugs (such as bevacizumab) showed variable efficacy, with ORRs of between 13% and 20%, and were especially useful in patients with contraindications to cytotoxic chemotherapy. The combination of everolimus with letrozole, for example, showed ORR of up to 32% in women with positive hormone receptors, suggesting benefit in specific tumor profiles.

These data reinforce the importance of a personalized therapeutic approach in advanced endometrial cancer, based on individual molecular and clinical characteristics, in order to optimize clinical outcomes and reduce the adverse effects associated with conventional therapies.

Immunotherapy in tumors with a high mutational load

Studies with pembrolizumab (anti-PD-1) in patients with high microsatellite instability (MSI-H) or DNA repair deficiency (dMMR) have shown ORR between 43% and 57%, with cases of durable response exceeding 2 years (OTT et al., 2017).

For microsatellite stable (MSS) tumors, the efficacy of immunotherapy alone was limited (ORR <10%), but studies combining pembrolizumab with lenvatinib (tyrosine-kinase inhibitor) showed ORRs of over 35%, with a median overall survival (OS) of 17.4 months (MAZZONI et al., 2022).

Promising therapeutic combinations

The KEYNOTE-775 clinical trial (Makker et al., 2022) showed that pembrolizumab + lenvatinib was significantly superior to standard second-line chemotherapy (doxorubicin or paclitaxel), with a 38% reduction in the risk of death and a 44% reduction in the risk of progression. Quality of life was maintained or improved in part of the patients who used immunotherapy, even in palliative settings, when compared to the hematological toxicity of conventional chemotherapy.

Toxicity profiles

mTOR inhibitors presented grade 3 or higher adverse events in 30% to 45% of patients, particularly hyperglycemia, mucositis and fatigue (SMITH et al., 2019). The combination of lenvatinib + pembrolizumab involved a higher incidence of hypertension, proteinuria and thyroid dysfunction, although clinical management was possible in most cases (MAKKER et al., 2022).

Adverse events

Immune-related events (such as colitis, pneumonitis and autoimmune hepatitis) have been reported in up to 17% of patients, requiring rescue corticosteroid therapy in some cases (DORSETT et al., 2021).

Impact of molecular classification

Molecular stratification based on The Cancer Genome Atlas (TCGA) has proven essential for personalizing treatment, with evidence that tumors with POLE or MSI-H mutations are more responsive to immunotherapy, while subtypes with chromosomal instability or mutated p53 respond better to chemotherapy combined with targeted therapies (LEON-CASTILLO et al., 2020).

Global outcomes

In patients with advanced endometrial cancer and eligible for targeted therapies, overall survival increased by between 3 and 8 months compared to traditional chemotherapy regimens alone, especially after the integration of immunotherapy into second-line treatment (SORENSEN et al., 2023).

These results support the current trend of therapeutic individualization based on molecular biomarkers, demonstrating that immunotherapy and targeted agents are reshaping the treatment landscape for advanced endometrial cancer, with significant gains in clinical response, time to progression and survival, especially in favourable molecular subgroups.

FINAL CONSIDERATIONS AND CONCLUSION

Advanced endometrial cancer represents one of the main challenges of contemporary oncogynecology, especially in patients with disease refractory to conventional chemotherapy. Recent advances in the field of molecular biology and immunotherapy have brought about a real transformation in the therapeutic approach to this neoplasm, allowing for more specific, effective and tolerable treatments.

The evidence presented in this systematic review indicates that molecular target therapies, such as mTOR inhibitors (everolimus, temsirolimus) and anti-angiogenic drugs (bevacizumab, lenvatinib), have modest efficacy when used alone, with response rates ranging from 10% to 20%. However, their combination with hormone therapy or immunotherapy has shown synergistic potential, increasing the clinical benefits.

Immunotherapy with immune checkpoint inhibitors, especially pembrolizumab, achieved significant clinical results in subgroups of patients with microsatellite instability (MSI-H) or DNA repair deficiency (dMMR), reaching response rates of over 45%. In addition, the combination of pembrolizumab and lenvatinib has established itself as a highly effective second-line therapeutic regimen, even in stable microsatellite tumors, with a direct impact on overall survival.

Another relevant aspect is the emerging role of molecular classification, especially that proposed by The Cancer Genome Atlas (TCGA), as a tool for risk stratification and treatment personalization. The identification of biomarkers such as PIK3CA, PTEN, POLE and p53 makes it possible not only to predict therapeutic response, but also to outline more precise and individualized management strategies.

However, it is important to note that most of the studies evaluated are phase II, with limitations related to sample size, heterogeneity of inclusion criteria and the absence of control groups in some cases. It is therefore necessary to carry out multicentre randomized phase III clinical trials which can confirm the superiority of these approaches over traditional

chemotherapy, as well as validating the use of biomarkers in clinical practice.

It is therefore concluded that molecular-targeted therapies and immunotherapy represent a promising and potentially transformative advance in the treatment of advanced endometrial cancer. The incorporation of therapeutic strategies based on the genetic and molecular characteristics of the tumor is fundamental to achieving better oncological results and providing patients with a better quality of life. Translating this evidence into clinical protocols requires effective integration between research, molecular diagnosis and patient-centered therapeutic decisions.

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