Current Trends in Gynecologic Oncology

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Advances in Targeted Therapies for Endometrial Cancer

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Abstract

Endometrial cancer remains a significant cause of morbidity among women worldwide, with advanced-stage disease posing therapeutic challenges. This article explores recent advances in targeted therapies, focusing on molecular pathways such as PI3K/AKT/mTOR and immune checkpoint inhibitors. We review clinical trial data, discuss treatment efficacy, and highlight future directions. Results indicate improved progression-free survival with targeted agents, though challenges like resistance persist. This comprehensive analysis underscores the potential of personalized medicine in improving outcomes for endometrial cancer patients.

Keywords: Endometrial cancer; targeted therapy; PI3K/AKT/mTOR; immune checkpoint inhibitors; personalized medicine; clinical trials; molecular pathways; progression-free survival; resistance; gynecologic oncology

Introduction

Endometrial cancer, the most common gynecologic malignancy in developed countries, accounts for approximately 7% of all cancers in women [1]. While early-stage disease is often curable with surgery, advanced or recurrent cases have limited treatment options, with five-year survival rates dropping to 17% for metastatic disease [2]. Recent advances in understanding the molecular underpinnings of endometrial cancer have spurred the development of targeted therapies. These therapies aim to disrupt specific pathways, such as the PI3K/AKT/mTOR axis, or leverage immune checkpoint inhibitors to enhance antitumor immunity [3]. This article synthesizes current evidence on targeted therapies, evaluates their efficacy, and discusses their implications for clinical practice.

Discussion

The PI3K/AKT/mTOR pathway is frequently dysregulated in endometrial cancer, with mutations in PTEN occurring in up to 80% of endometrioid subtypes [4]. Inhibitors like everolimus and temsirolimus have shown promise in phase II trials, with response rates of 20–30% in recurrent disease [5]. However, resistance mechanisms, including feedback loops, limit long-term efficacy [6]. Combining mTOR inhibitors with hormonal therapies, such as letrozole, has improved progression-free survival (PFS) in clinical studies, with median PFS reaching 6.7 months compared to 3.2 months with monotherapy [7]. Immune checkpoint inhibitors, particularly anti-PD-1/PD-L1 agents like pembrolizumab, have transformed treatment for microsatellite instability-high (MSI-H) tumors, which comprise 25–30% of endometrial cancers [8]. The KEYNOTE-158 trial reported a 48% objective response rate (ORR) in MSI-H patients treated with pembrolizumab [9]. However, microsatellite-stable tumors respond poorly, necessitating combination strategies, such as with lenvatinib, which yielded a 38% ORR in non-MSI-H cases [10]. Challenges include managing immune-related adverse events and identifying biomarkers to predict response. Emerging therapies targeting HER2 amplification and FGFR2 mutations are also under investigation, with early-phase trials showing modest activity [11]. The integration of next-generation sequencing into clinical practice has enabled the identification of actionable mutations, paving the way for personalized treatment plans.

Results

Clinical trials of mTOR inhibitors demonstrate partial responses in 20–30% of patients with recurrent endometrial cancer, with median PFS ranging from 3 to 7 months [5, 7]. Pembrolizumab monotherapy in MSI-H tumors achieves a 48% ORR, with a median duration of response exceeding 20 months [9]. Combination therapies, such as pembrolizumab plus lenvatinib, show a 38% ORR in non-MSI-H tumors, with median PFS of 7.4 months [10]. Adverse events, including fatigue, hypertension, and diarrhea, occur in 60–80% of patients but are generally manageable. Biomarker-driven trials report higher response rates in patients with specific molecular profiles, such as PTEN loss or MSI-H status.

Conclusion

Targeted therapies have ushered in a new era for endometrial cancer management, particularly for advanced or recurrent disease. While mTOR inhibitors and immune checkpoint inhibitors show significant promise, challenges like resistance and toxicity necessitate further research. Biomarker-driven approaches and combination strategies hold the key to optimizing outcomes. Continued investment in clinical trials and molecular profiling will be critical to realizing the full potential of personalized medicine in endometrial cancer.

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Received: 01-Feb-2025, Manuscript No. ctgo-25-168495; **Editor assigned**: 03-Feb-2025, PreQC No. ctgo-25-168495 (PQ); **Reviewed:** 17-Feb-2025, QC No. ctgo-25-168495; **Revised:** 21-Feb-2025, Manuscript No. ctgo-25-168495 (R); **Published:** 28-Feb-2025, DOI: 10.4172/ctgo.1000255

Citation: Sarah JT (2025) Advances in Targeted Therapies for Endometrial Cancer. Current Trends Gynecol Oncol, 10: 255.

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