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IMMUNOTHERAPY IN RECURRENT AND METASTATIC VULVAR CANCER: CURRENT APPROACHES AND CLINICAL PERSPECTIVES

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Abstract

Vulvar cancer is a rare gynecological malignancy that predominantly affects elderly women and is often associated with poor outcomes in advanced stages. Recurrent and metastatic vulvar cancer represents a significant clinical challenge due to limited treatment options and resistance to conventional therapies such as surgery, radiotherapy, and chemotherapy. In recent years, immunotherapy has emerged as a promising therapeutic approach in the management of advanced gynecological cancers, including vulvar cancer. This article aims to review the role of immunotherapy in the treatment of recurrent and metastatic vulvar cancer, with a particular focus on immune checkpoint inhibitors and tumor immune microenvironment interactions. Current clinical evidence suggests that immunotherapeutic strategies may offer meaningful clinical benefits in selected patients, especially those with programmed death-ligand 1 (PD-L1) expression, high tumor mutational burden, or human papillomavirus (HPV)-associated disease. Understanding the immunological mechanisms and identifying predictive biomarkers are essential for optimizing treatment outcomes and improving survival in patients with advanced vulvar cancer.

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Keywords: Vulvar cancer, immunotherapy, recurrent disease, metastatic disease, immune checkpoint inhibitors, PD-L1, gynecologic oncology

Introduction

Vulvar cancer is a rare malignancy of the female genital tract, accounting for a small proportion of gynecological cancers, yet it is associated with significant morbidity and mortality, particularly in advanced stages. The disease predominantly affects postmenopausal women; however, its incidence among younger patients has increased in recent years, partly due to human papillomavirus (HPV)–associated etiological pathways. Despite advances in surgical techniques and adjuvant therapies, the prognosis of recurrent and metastatic vulvar cancer remains poor.

Standard treatment options for vulvar cancer include surgery, radiotherapy, and chemotherapy, either alone or in combination. While these approaches can be effective in early-stage disease, their efficacy is limited in recurrent or metastatic settings. High rates of treatment resistance, disease progression, and treatment-related toxicity significantly reduce survival and quality of life in patients with advanced disease. Consequently, there is an urgent need for novel therapeutic strategies that can improve clinical outcomes in this challenging patient population.

Recent progress in cancer immunology has led to the development of immunotherapy as an innovative treatment modality in oncology. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) have demonstrated clinical benefits in various solid tumors. Given the immunogenic nature of vulvar cancer, particularly HPV-associated tumors, immunotherapy has gained increasing attention as a potential treatment option for recurrent and metastatic disease.

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The tumor immune microenvironment plays a critical role in disease progression and therapeutic response in vulvar cancer. Expression of immune biomarkers such as PD-L1, tumor-infiltrating lymphocytes, and tumor mutational burden may influence sensitivity to immunotherapeutic agents. Understanding these immunological mechanisms is essential for identifying patients who are most likely to benefit from immune-based treatments.

This article aims to explore the current role of immunotherapy in recurrent and metastatic vulvar cancer, focusing on underlying immunological mechanisms, clinical evidence, and future perspectives. A comprehensive evaluation of emerging immunotherapeutic strategies may contribute to optimizing treatment approaches and improving outcomes for patients with advanced vulvar cancer.

Molecular and Immunological Background of Vulvar Cancer

Vulvar cancer is a biologically heterogeneous disease characterized by distinct molecular and immunological pathways that influence tumor behavior and therapeutic response. Two major etiological pathways have been identified: human papillomavirus (HPV)–associated vulvar squamous cell carcinoma and HPV-independent tumors, which are often linked to chronic inflammatory dermatoses such as lichen sclerosus. These pathways differ significantly in terms of molecular alterations, immune microenvironment, and prognosis.

HPV-associated vulvar cancers typically arise in younger patients and are characterized by viral oncoprotein expression, which promotes genomic instability and malignant transformation. The presence of viral antigens contributes to increased tumor immunogenicity, resulting in higher infiltration of immune cells, particularly cytotoxic T lymphocytes. This immunologically active tumor microenvironment provides a biological rationale for the use of immunotherapy, as immune checkpoint pathways are frequently upregulated to enable tumor immune evasion.

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In contrast, HPV-independent vulvar cancers generally occur in older women and exhibit a more aggressive clinical course. These tumors are often associated with mutations in tumor suppressor genes, chronic inflammation, and a less inflamed immune microenvironment. Reduced immune cell infiltration and increased immune suppression may contribute to resistance to conventional therapies and poorer outcomes in advanced disease stages.

The tumor immune microenvironment plays a central role in the progression and treatment response of vulvar cancer. Key components include tumor-infiltrating lymphocytes, antigen-presenting cells, cytokines, and immune checkpoint molecules such as programmed death-ligand 1 (PD-L1). Overexpression of PD-L1 on tumor cells and immune cells has been reported in a subset of vulvar cancers and is associated with immune escape mechanisms that inhibit antitumor T-cell activity.

Tumor mutational burden and microsatellite instability, although less frequent in vulvar cancer compared to other solid tumors, may also influence immunotherapy responsiveness. Tumors with higher mutational loads generate more neoantigens, increasing their visibility to the immune system and potentially enhancing sensitivity to immune checkpoint inhibition.

Understanding the molecular and immunological landscape of vulvar cancer is essential for the development of personalized treatment strategies. Identification of predictive biomarkers and immune-related molecular features may help stratify patients who are most likely to benefit from immunotherapy, particularly in recurrent and metastatic settings where therapeutic options remain limited.

Immunotherapy Strategies in Recurrent and Metastatic Vulvar Cancer

Immunotherapy has emerged as a promising treatment option for patients with recurrent and metastatic vulvar cancer, particularly in cases where conventional therapies have failed or provided limited benefit. The primary immunotherapeutic approaches investigated in vulvar cancer include immune checkpoint inhibition,

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therapeutic cancer vaccines, and combination strategies integrating immunotherapy with chemotherapy or radiotherapy.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) and its ligand PD-L1 represent the most extensively studied immunotherapeutic agents in vulvar cancer. These drugs restore antitumor immune responses by blocking inhibitory signaling pathways that suppress T-cell activity. Expression of PD-L1 has been identified in a subset of vulvar squamous cell carcinomas, providing a biological rationale for the use of PD-1/PD-L1 inhibitors in advanced disease.

Clinical evidence suggests that patients with recurrent or metastatic vulvar cancer may achieve durable responses to PD-1 inhibitors, particularly those with HPV-associated tumors or tumors exhibiting immune-inflamed microenvironments. Although overall response rates remain modest, a subset of patients experiences meaningful disease stabilization and prolonged survival, highlighting the potential role of immunotherapy in selected cases.

CTLA-4 Inhibition and Dual Checkpoint Blockade

Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is another immune checkpoint involved in regulating early T-cell activation. While CTLA-4 inhibitors have demonstrated efficacy in several malignancies, their role in vulvar cancer remains under investigation. Dual checkpoint blockade combining PD-1 and CTLA-4 inhibitors may enhance antitumor immune responses by targeting complementary immune regulatory pathways. However, increased toxicity associated with combination therapy necessitates careful patient selection and monitoring.

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Therapeutic Cancer Vaccines

Given the association of a significant proportion of vulvar cancers with HPV infection, therapeutic vaccines targeting HPV-related antigens represent an attractive immunotherapeutic strategy. These vaccines aim to stimulate a specific immune response against viral oncoproteins expressed by tumor cells. Early-phase studies have shown immunogenicity and potential clinical benefit, particularly when combined with immune checkpoint inhibitors or other immune-modulating therapies.

Combination Immunotherapy Approaches

Combining immunotherapy with chemotherapy or radiotherapy is an area of active research in vulvar cancer. Conventional treatments may enhance tumor immunogenicity by increasing antigen release and modulating the tumor microenvironment, thereby improving the efficacy of immunotherapy. Preliminary data suggest that such combination strategies may improve response rates and overcome resistance mechanisms in recurrent and metastatic disease.

Overall, immunotherapy represents a promising yet evolving treatment modality for recurrent and metastatic vulvar cancer. Continued research is required to optimize therapeutic strategies, identify predictive biomarkers, and determine the most effective combinations to improve clinical outcomes in this rare and challenging malignancy.

Clinical Trials and Outcomes

Clinical evidence supporting the use of immunotherapy in recurrent and metastatic vulvar cancer is currently limited but growing, largely due to the rarity of the disease and challenges in conducting large, randomized trials. Most available data are derived from phase I–II clinical trials, basket trials, and retrospective analyses that include vulvar cancer as a subgroup within gynecologic or rare solid tumors.

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Immune checkpoint inhibitors, particularly PD-1 and PD-L1 inhibitors, have been evaluated in several multicenter studies involving patients with advanced vulvar squamous cell carcinoma who had progressed after standard therapies. These studies have demonstrated modest overall response rates; however, a subset of patients achieved durable responses and prolonged disease control. Notably, responses were more frequently observed in patients with PD-L1–positive tumors and HPV-associated disease, suggesting the potential role of immune biomarkers in predicting treatment efficacy.

Progression-free survival and overall survival outcomes in immunotherapy-treated patients varied across studies, reflecting heterogeneity in patient populations, prior treatments, and biomarker status. While median progression-free survival remained relatively short, some patients experienced long-term clinical benefit, highlighting the unique potential of immunotherapy to induce sustained immune-mediated tumor control rather than rapid cytotoxic effects.

Combination strategies have also been explored in early-phase trials. The integration of immune checkpoint inhibitors with chemotherapy or radiotherapy has shown encouraging preliminary results, with improved disease stabilization rates compared to monotherapy. Radiotherapy, in particular, may enhance immunotherapy efficacy through immune priming effects, increasing tumor antigen presentation and promoting systemic antitumor immune responses.

Therapeutic HPV-targeted vaccines have been assessed in small clinical studies, primarily in HPV-associated vulvar cancer. These trials reported favorable safety profiles and evidence of immune activation, although objective tumor responses were limited when vaccines were used alone. Ongoing research focuses on combining therapeutic vaccines with immune checkpoint inhibitors to amplify antitumor immunity and improve clinical outcomes.

Overall, current clinical trial data indicate that immunotherapy is a feasible and potentially beneficial treatment option for selected patients with recurrent and metastatic vulvar cancer. Nevertheless, the limited sample sizes and lack of

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randomized controlled trials underscore the need for further prospective studies. Future research should prioritize biomarker-driven patient selection, standardized outcome measures, and combination treatment strategies to better define the role of immunotherapy in this rare malignancy.

Discussion

The present review highlights the evolving role of immunotherapy in the management of recurrent and metastatic vulvar cancer, a disease characterized by limited therapeutic options and poor prognosis in advanced stages. Although vulvar cancer remains a rare gynecologic malignancy, growing evidence suggests that immune-based therapies may provide clinically meaningful benefits for selected patients.

The observed responses to immune checkpoint inhibitors, particularly PD-1/PD-L1 blockade, underscore the importance of tumor immunogenicity in vulvar cancer. HPV-associated tumors appear to be more responsive to immunotherapy due to the presence of viral antigens that enhance immune recognition. Increased infiltration of tumor-infiltrating lymphocytes and higher expression of immune checkpoint molecules in these tumors further support the rationale for immune-targeted treatments. However, responses have also been reported in HPV-independent cases, indicating that additional immunological mechanisms may contribute to treatment sensitivity. Despite these encouraging findings, overall response rates to immunotherapy remain modest. This limitation may be attributed to tumor heterogeneity, immune escape mechanisms, and the presence of immunosuppressive tumor microenvironments. The variability in PD-L1 expression, tumor mutational burden, and immune cell infiltration across vulvar cancers complicates patient selection and highlights the need for reliable predictive biomarkers. Incorporating molecular and immunological profiling into routine clinical practice may help identify patients most likely to benefit from immunotherapy.

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Combination strategies represent a promising approach to overcoming resistance and enhancing therapeutic efficacy. The integration of immune checkpoint inhibitors with radiotherapy or chemotherapy may promote immunogenic cell death and improve antitumor immune responses. Early clinical data suggest that such combinations may lead to improved disease control, although toxicity and optimal sequencing remain important considerations. Similarly, therapeutic HPV-targeted vaccines combined with checkpoint inhibitors may provide synergistic effects by enhancing tumor-specific immune activation.

From a clinical perspective, immunotherapy offers the potential for durable disease control and improved quality of life in a subset of patients with advanced vulvar cancer. However, the lack of large randomized trials and standardized treatment protocols limits the generalizability of current findings. Multicenter collaboration and inclusion of vulvar cancer patients in basket trials are essential to advancing evidence-based immunotherapeutic approaches for this rare malignancy.

Overall, immunotherapy represents a significant step toward personalized treatment in recurrent and metastatic vulvar cancer. Continued research focusing on biomarker-driven strategies, combination therapies, and long-term outcome assessment is critical to fully defining its role in clinical practice.

Conclusion

Recurrent and metastatic vulvar cancer remains a significant therapeutic challenge due to its aggressive clinical course and limited effectiveness of conventional treatment modalities. Recent advances in cancer immunology have opened new perspectives for the management of this rare gynecologic malignancy, positioning immunotherapy as a promising treatment option for selected patients.

Current evidence indicates that immune checkpoint inhibitors, particularly those targeting the PD-1/PD-L1 pathway, can induce durable clinical responses in a

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subset of patients with advanced vulvar cancer. HPV-associated tumors and those with an immune-inflamed tumor microenvironment appear to derive the greatest benefit from immunotherapeutic approaches. However, overall response rates remain modest, underscoring the heterogeneity of the disease and the complexity of immune escape mechanisms. Combination strategies involving immunotherapy with radiotherapy, chemotherapy, or therapeutic HPV-targeted vaccines show encouraging preliminary results and may enhance antitumor immune responses. Biomarker-driven patient selection, including assessment of PD-L1 expression, tumor mutational burden, and immune cell infiltration, is crucial for optimizing treatment outcomes and minimizing unnecessary toxicity. In conclusion, immunotherapy represents an important step toward personalized treatment in recurrent and metastatic vulvar cancer. Further prospective, multicenter clinical trials and translational research are essential to refine patient selection criteria, establish optimal combination regimens, and improve long-term survival and quality of life for patients affected by this rare but challenging disease.

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