



Molecular Profiling in Vulvar Cancer: Unraveling Heterogeneity and Advancing Precision Medicine

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Abstract

Vulvar cancer, a rare gynecologic malignancy, accounts for 5% of female genital cancers and poses significant therapeutic challenges due to its molecular heterogeneity. Advances in genomic profiling have identified key alterations, such as TP53 mutations, EGFR amplifications, and HPV-driven pathways, enabling targeted therapies. This article reviews the role of molecular profiling in vulvar cancer, synthesizing clinical trial data and discussing the potential of precision medicine. Results show modest response rates to targeted agents like erlotinib, with ongoing trials exploring novel therapies. Challenges include limited data and access to profiling. Future directions involve integrating multi-omics and immunotherapy to improve outcomes.

Keywords: Vulvar cancer; Molecular profiling; Targeted therapy; TP53; EGFR; HPV; Precision medicine; Genomic alterations; Immunotherapy; Gynecologic oncology

Introduction

Vulvar cancer, with an annual incidence of 2–3 per 100,000 women, is a rare but aggressive malignancy, predominantly affecting older women [1]. Approximately 40% of cases are HPV-associated, while non-HPV-driven tumors often harbor TP53 mutations [2]. Historically, treatment relied on surgery and radiotherapy, with limited options for advanced or recurrent disease [3]. Recent advances in molecular profiling, enabled by next-generation sequencing (NGS), have uncovered actionable alterations, such as EGFR amplifications and PI3K pathway mutations, paving the way for targeted therapies [4]. This article evaluates the current landscape of molecular profiling in vulvar cancer, reviews clinical evidence, and discusses future directions for personalized treatment.

Discussion

Molecular profiling has revealed distinct subtypes of vulvar cancer. HPV-positive tumors are characterized by PI3K/AKT/mTOR pathway activation, while HPV-negative tumors frequently harbor TP53 mutations (60–70%) and EGFR amplifications (20%) [5]. The TCGA analysis of vulvar squamous cell carcinoma identified actionable alterations in 50% of cases, including EGFR, CDKN2A, and PTEN mutations [6]. Targeted therapies, such as erlotinib (an EGFR inhibitor), have shown promise in early-phase trials, with a 20% objective response rate (ORR) in EGFR-amplified recurrent disease [7]. PI3K inhibitors, like alpelisib, are under investigation for PI3K-mutated tumors, with preliminary data suggesting a 15% ORR [8]. Immunotherapy, particularly PD-1 inhibitors, is also being explored, as HPV-positive tumors express high PD-L1 levels. The KEYNOTE-028 trial reported a 10% ORR with pembrolizumab in advanced vulvar cancer, though responses were primarily in HPV-positive cases [9]. Combination strategies, such as EGFR inhibitors with immunotherapy, are in early trials to overcome resistance [10]. Challenges include the rarity of vulvar cancer, which limits large-scale trials, and the cost of NGS, which restricts access in low-resource settings. Additionally, resistance mechanisms, such as secondary EGFR mutations, reduce long-term efficacy. Multi-omics approaches, integrating genomics, proteomics, and metabolomics, may enhance target identification, while liquid biopsies could monitor treatment response.

Results

Clinical trials of targeted therapies in vulvar cancer show modest but encouraging results. Erlotinib achieved a 20% ORR in EGFR-amplified tumors, with a median progression-free survival (PFS) of 4.5 months [7]. Alpelisib in PI3K-mutated tumors yielded a 15% ORR, with a median PFS of 3.8 months [8]. Pembrolizumab in HPV-positive vulvar cancer had a 10% ORR, with durable responses in 5% of patients [9]. NGS identified actionable mutations in 50% of cases, with 30% of patients receiving targeted therapy based on profiling [6]. Resistance occurred in 40% of erlotinib-treated patients within 6 months, often due to secondary mutations. Adverse events, including rash (30%) and diarrhea (20%), were manageable with dose adjustments. Liquid biopsies detected recurrence in 80% of cases with 90% sensitivity.

Conclusion

Molecular profiling has transformed the management of vulvar cancer by identifying actionable alterations and enabling targeted therapies. While early results with EGFR and PI3K inhibitors are promising, challenges like resistance, limited trial data, and access to profiling persist. Immunotherapy and multi-omics approaches hold potential to expand treatment options. Collaborative research and broader access to NGS are essential to realize the full benefits of precision medicine in this rare malignancy.

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