A Comprehensive Review of Overcoming Resistance to Anti-Angiogenesis Pharmacotherapy in Pediatric Sarcomas

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Abstract:

Pediatric sarcomas comprise a heterogeneous group of malignant mesenchymal neoplasms that heavily rely on angiogenesis for tumor growth, invasion, and metastasis. Despite advances in anti-angiogenic pharmacotherapy, including agents targeting vascular endothelial growth factor (VEGF) and its receptors, therapeutic efficacy remains compromised by the rapid emergence of resistance. This comprehensive review outlines the multifaceted molecular and cellular mechanisms underlying resistance to anti-angiogenic therapies in pediatric sarcomas. Key mechanisms include the compensatory upregulation of alternative pro-angiogenic factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and angiopoietin-2 (Ang-2); adaptive remodeling of the tumor vasculature through processes such as vascular co-option and mimicry; and the recruitment of pro-angiogenic stromal cells, including pericytes, myeloid-derived suppressor cells, and cancer-associated fibroblasts. Furthermore, tumor hypoxia-driven activation of hypoxia-inducible factors (HIFs) orchestrates metabolic reprogramming and immune evasion, which contribute to therapeutic failure. We explore current and emerging strategies designed to overcome these resistance pathways, emphasizing rational combination therapies that integrate anti-VEGF agents with immune checkpoint inhibitors, multi-target tyrosine kinase inhibitors, and modulators of the tumor microenvironment. The review also highlights the significance of predictive biomarkers, including circulating angiogenic factors and gene expression signatures, in informing personalized treatment and adaptive therapy protocols. Finally, advances in dosing regimens, including metronomic scheduling and chronotherapy, are discussed for their potential to enhance vascular normalization and improve drug delivery. A thorough understanding of resistance mechanisms and the integration of biomarker-driven therapeutic strategies are imperative to optimizing anti-angiogenic pharmacotherapy and enhancing clinical outcomes in pediatric sarcoma patients.

Keywords: Angiogenic proteins; Angiogenesis Inhibitors; Drug resistance; Clinical practice guideline; Vascular Endothelial Growth Factors.