

Biomarkers Predicting Response to Antiangiogenic Agents: Personalized Medicine in Practice

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Introduction

The emergence of antiangiogenic therapies marked a turning point in oncology, introducing the concept of targeting the tumor microenvironment rather than the tumor cells alone. These therapies, aimed at disrupting the blood vessel networks that supply nutrients and oxygen to tumors, have been incorporated into treatment regimens for various cancers, including colorectal, renal, lung, breast, and ovarian carcinomas. Agents targeting Vascular Endothelial Growth Factor (VEGF) and its receptors (VEGFRs), Platelet-Derived Growth Factor Receptors (PDGFRs), and angiopoietin/Tie pathways have shown clinical success in extending progression-free survival and, in some cases, overall survival [1].

However, despite their initial promise, the therapeutic benefits of antiangiogenic agents have been modest and often short-lived in many patients. A significant challenge has been the absence of validated predictive biomarkers that can guide patient selection and monitor therapeutic response. Tumor heterogeneity, complex angiogenic signaling, and adaptive resistance mechanisms further complicate treatment outcomes [2].

Description

Circulating proteins, cells, or nucleic acids in blood or plasma offer a non-invasive method to assess the systemic effects of therapy. VEGF-A is the most well-studied proangiogenic cytokine. Elevated baseline levels have been associated with poor prognosis in many cancers. In some studies, high VEGF-A levels correlate with response to bevacizumab in metastatic colorectal cancer (mCRC), although findings are inconsistent across tumor types. sVEGFR-1 acts as a decoy receptor, sequestering VEGF. A high sVEGFR-1 level has been correlated with reduced response to bevacizumab, while sVEGFR-2 levels decrease after antiangiogenic treatment, possibly indicating on-target activity. PlGF levels often increase following VEGF blockade, suggesting its role in adaptive resistance. Rising PlGF levels during treatment have been associated with poor outcomes, but its utility as a predictive marker remains under investigation [3].

Molecular profiling of tumor biopsies offers direct information about the tumor's angiogenic status and responsiveness. High VEGF or VEGFR expression in tumor tissue has been inconsistently associated with response to

antiangiogenic agents. The heterogeneity of VEGF isoforms and their temporal expression limits reliability. Hypoxia-inducible factor 1-alpha (HIF-1 α) and carbonic anhydrase IX (CAIX) are overexpressed in hypoxic tumor regions. Their presence often correlates with increased angiogenic drive and resistance to VEGF blockade. High Ang-2 or low Ang-1 expression levels may indicate poor vessel stability and greater reliance on VEGF signaling, potentially predicting sensitivity to combined VEGF/Ang-2 inhibitors [4].

Combining genomic, transcriptomic, proteomic, and metabolomic data provides a holistic view of the tumor and its angiogenic dependencies. Machine learning models can identify composite biomarkers predictive of response. Circulating tumor DNA (ctDNA), extracellular vesicles, and exosomal RNA offer non-invasive, repeatable means to track angiogenic signaling and resistance evolution. As antiangiogenic agents are increasingly combined with immune checkpoint inhibitors and targeted therapies, identifying predictive biomarkers for these regimens is crucial. Serial assessments of biomarkers during treatment can provide early insights into therapeutic efficacy and resistance, guiding timely modifications [5].

Conclusion

The promise of antiangiogenic therapies in cancer treatment lies not only in their ability to disrupt tumor vasculature but in their integration into precision medicine. Biomarkers that predict response to these agents offer the key to unlocking their full potential, guiding patient selection, monitoring efficacy, and informing adaptive therapeutic strategies. While no single biomarker has yet proven universally predictive, a growing body of research suggests that multifactorial, dynamic, and integrated biomarker approaches hold the greatest promise. Future progress will depend on the standardization of biomarker assays, large-scale prospective validation, and continued investment in translational oncology. As the era of personalized medicine matures, the identification of robust predictive biomarkers for antiangiogenic agents will be instrumental in transforming cancer care-shifting from one-size-fits-all to a more nuanced, tailored approach that maximizes benefit and minimizes harm.

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Conflict of Interest

None.

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