

Breaking the barrier: a guidelines-based review of antiangiogenesis drug resistance in pediatric cancer therapy

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The growth and metastatic potential of most solid and hematological tumors are angiogenesis-dependent. Antiangiogenic therapies have demonstrated clinical advantages in the treatment of numerous tumor types. Nevertheless, resistance to antiangiogenic therapy has emerged over time. This study aimed to review physiological blood vessel growth, angiogenesis, tumor vasculature, the role of vascular endothelial growth factor and its receptor in tumor angiogenesis, antiangiogenesis, resistance to antiangiogenic therapy, and mechanisms of resistance to antiangiogenic treatment while also providing guidance for the development of antiangiogenic therapies. We reviewed Google Scholar and PubMed for studies examining antiangiogenesis therapy, resistance to antiangiogenic agents, and strategies for overcoming them, thereby creating a guidelines-based approach. This review discusses a novel adaptive resistance mechanism involving metabolic adaptability of tumor cells. We found that personalized medicine may enhance the angiogenic mechanisms utilized by tumors. Thus, antiangiogenic therapy should be personalized by incorporating insights into tumor-specific vascularization and metabolism along with biomarker-guided treatment strategies. In addition to developing new pharmaceuticals, we must prioritize the identification of reliable markers for pathway activation and response. Addressing these challenges enables the optimization of antiangiogenic treatments within a precision oncology framework, thereby enhancing the prediction of therapeutic benefits and minimizing the risk of resistance in pediatric malignancies. In addition to conventional or salvage chemotherapy, antiangiogenic agents may serve as adjunctive chemotherapeutic agents, particularly for solid tumors. We also provide a guidelines-based approach to pediatric cancer therapy using antiangiogenic agents in countries with limited resources.

Key words: Angiogenic proteins, Angiogenesis inhibitors, Drug resistance, Clinical practice guidelines, Vascular endothelial growth factor

Key message

Antiangiogenic therapy resistance in pediatric cancers involves alternative angiogenic pathways, microenvironmental support, hypoxia-driven signaling, metabolic reprogramming, and structural adaptations such as vascular co-option. Metabolic adaptation highlights tumor plasticity. Effective treatments combine immunotherapy with biomarkers. To address vascular endothelial growth factor limitations, emerging targets include hypoxia-inducible factor-2 α , endoglin, CXCR4, angiopoietin/Tie2, and bispecific antibodies. In resource-constrained settings, the guidelines recommend low-dose chemotherapy plus oral multiantiangiogenic agents to ensure improved accessibility and treatment outcomes.

Physiology of blood vessel development

During embryonic development, blood vessels form through a series of coordinated processes including vasculogenesis, sprouting angiogenesis, arteriogenesis, intussusceptive angiogenesis, and looping angiogenesis.¹⁻⁴ Vasculogenesis initiates de novo vessel formation from angioblasts, whereas sprouting angiogenesis involves the vascular endothelial growth factor (VEGF)-driven growth of new branches from existing vessels. Arteriogenesis remodels capillaries into mature arteries and veins with assistance from pericytes and smooth muscle cells.^{4,5} Intussusception involves the division of existing vessels through internal structural remodeling, whereas looping

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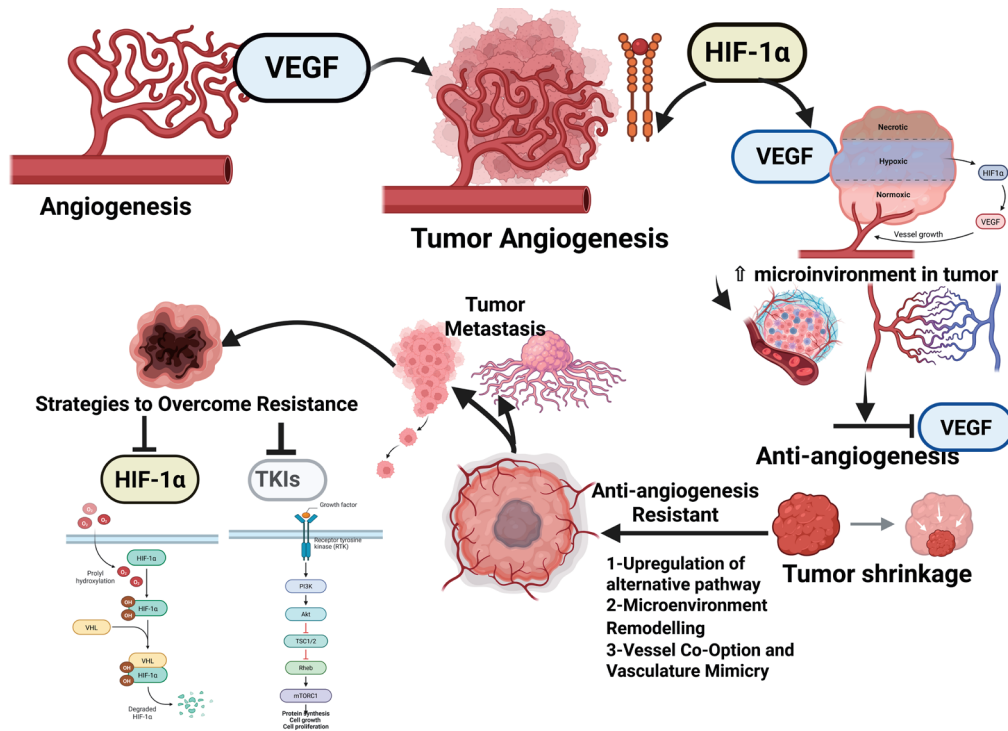
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Graphic abstract. VEGF, vascular endothelial growth factor; HIF-1 α , hypoxia-inducible factor 1 α ; TKI, tyrosine kinase inhibitor.

angiogenesis recruits preexisting vessels to tissue repair sites. These processes are regulated by a balance between pro- and antiangiogenic factors, and essential for proper vascular development.⁶⁻⁸⁾

Angiogenesis in cancer

Tumors hijack normal angiogenesis to support their growth, leading to abnormal and inefficient blood vessel formation. This process begins with hypoxia-induced VEGF release, which causes excessive sprouting angiogenesis and disorganized leaky vessels.⁹⁻¹²⁾ Tumor-derived signals also recruit bone marrow cells that sustain angiogenesis through cytokine secretion. Intussusceptive angiogenesis enables rapid vessel remodeling, whereas vasculogenic mimicry allows tumor cells to form vessel-like structures without requiring endothelial cells. Additionally, tumors may grow by co-opting existing blood vessels in the surrounding tissue. Taken together, these mechanisms enable tumors to secure a blood supply, promote invasion, and resist treatment.^{5,13-18)}

Proangiogenic pathways in pediatric cancers

Angiogenesis is crucial for the growth, invasion, and metastasis of pediatric solid tumors including neuroblastoma

(NB), Wilms' tumors, and sarcomas. These cancers secrete VEGF and other growth factors that stimulate new blood vessel formation. Tumor hypoxia stabilizes hypoxia-inducible factor-1 α (HIF-1 α), which upregulates VEGF and other proangiogenic genes.¹⁹⁾ Pediatric tumors frequently show an "angiogenic switch characterized by increased levels of VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), angiopoietins, and matrix-degrading enzymes. High microvessel density and elevated circulating angiogenic cytokines are characteristics of pediatric solid tumors and leukemia, indicating that angiogenesis is a key driver of disease progression. Inflammatory mediators, such as granulocyte-macrophage colony-stimulating factor, tumor necrosis factor alpha, transforming growth factor beta (TGF- β), interferon gamma, interleukin-8 (IL-8), also known as CXCL8, and platelet-activating factor, further influence this process.^{19,20)}

Key mediators of angiogenesis

Several key pathways drive angiogenesis in pediatric cancers. The VEGF/VEGF receptor (VEGF/VEGFR) pathway is central, with VEGF-A promoting endothelial proliferation, survival, and vessel permeability.^{20,21)} Most pediatric tumors, including NB, Wilms' tumor, and medulloblastoma (MB), express VEGF, high levels of which are often correlated with metastasis and a poor prognosis. Although

anti-VEGF agents such as bevacizumab reduce vascularity, resistance can develop through alternate pathways. HIF-1 α , activated by hypoxia, induces the expression of VEGF and other proangiogenic genes (e.g., FGF-2, PDGF-B, angiopoietins), thereby contributing to tumor survival and therapy resistance.²²⁻²⁴⁾

Herpes simplex virus type 1 induces angiogenesis owing to the presence of large CpG copies, which are themselves angiogenic and may therefore be of interest for gene therapy.²⁵⁾ FGF-2, which is often coexpressed with VEGF, enhances angiogenesis by stimulating endothelial and perivascular cell growth. Similarly, PDGF-BB activates PDGFR on pericytes, thereby stabilizing vessels and promoting tumor progression in cancers such as NB and sarcoma. The angiopoietin/Tie2 pathway regulates vessel maturation, with angiopoietin-2 (Ang-2) promoting vessel destabilization and sprouting. Elevated Ang-2 levels are associated with aggressive disease and poor outcomes. Notch signaling, particularly the delta-like ligand 4 (DLL4)/Notch interactions, controls the behavior of tip and stalk cells during sprouting, and blocking DLL4 leads to excessive but nonfunctional vessels.^{26,27)} Tumors exploit this feedback loop to fine-tune angiogenesis, and the dual inhibition of VEGF and DLL4 is under investigation. Additional mediators include CXCL8/IL-8, endothelins, adipokines, and matrix metalloproteinases,^{5,26,27)} which promote endothelial migration, matrix degradation, and VEGF-independent angiogenesis. Integrins such as $\alpha_v\beta_3$ also aid in vessel sprouting. Together, these overlapping pathways create a robust proangiogenic environment in pediatric tumors, supporting their growth, invasion, and resistance.^{21,22,27,28)}

Angiogenesis in specific pediatric cancers

1. Neuroblastoma

NB, the most common extracranial solid tumor in children, exhibits high vascular density and hypoxia and reflects vigorous angiogenic activity. NB cells and their microenvironment secrete VEGF, FGF, and PDGF, driven mainly by HIF-1 α /2 α under hypoxic conditions. High HIF levels are associated with advanced disease and poor clinical outcomes. While VEGF expression may be associated with cell differentiation and better prognosis, aggressive NB is generally highly angiogenic, and microvessel density correlates with disease progression. Tumor-associated macrophages (TAM) contribute to an immunosuppressive and proangiogenic environment, while elevated VEGF levels and VEGFR expression are associated with metastasis.^{21,29-31)} Although bevacizumab has been tested in trials such as the BEACON-Neuroblastoma, it

was not shown to significantly improve survival, likely due to compensatory angiogenic pathways.³²⁾ Multitarget tyrosine kinase inhibitors (TKIs) such as pazopanib and cabozantinib have shown promise in preclinical models by inhibiting VEGF, PDGF, and MET signaling. New approaches, including PI3K/BRD4 inhibitors and stromal-targeting agents such as L19, aim to more effectively suppress angiogenesis. Overall, while VEGF is a key driver, overcoming angiogenic resistance in NB likely requires multi-targeted or combination therapies rather than VEGF inhibition alone.^{21,22,29-31,33)}

2. MB and other central nervous system tumors

MB, the most common malignant brain tumor in children, is highly vascularized, and both angiogenesis and lymphangiogenesis contribute to its growth and spread, particularly through the cerebrospinal fluid. VEGF-A is especially elevated in aggressive subtypes such as Sonic Hedgehog and large-cell/anaplastic MB, whereas VEGF-C and the VEGFR-3 axis drive lymphatic involvement in groups 3 and 4. High VEGF expression and microvessel density are correlated with a poor prognosis and higher relapse risk.²²⁾ Clinically, angiogenic markers such as VEGF are being explored for risk stratification using tools such as perfusion magnetic resonance imaging. MB subtypes differ in angiogenic dependence: group 3 is highly angiogenic and metastatic, while WNT tumors are less so, suggesting a subgroup-specific responsiveness to antiangiogenic therapy. Although anti-VEGF monotherapies such as bevacizumab have shown limited benefits in high-grade gliomas (e.g., ACNS0822 trial), they are effective in pediatric low-grade glioma (PLGG), particularly for preserving vision in optic pathway gliomas. In MB, the most promising approach is metronomic therapy as demonstrated by the metronomic multiagent antiangiogenic therapy (MEMMAT) regimen,³⁴⁾ which combines low-dose chemotherapy with multiple antiangiogenic agents. This strategy achieved long-term survival in a subset of patients with relapsed MB, particularly in groups 3 and 4. Newer therapies, such as TKIs (e.g., axitinib), are also being studied. Overall, MB's reliance on angiogenesis supports the use of integrated treatment strategies that combine anti-VEGF agents with immunotherapy, TKIs, or lymphangiogenesis inhibitors to improve outcomes and personalize therapy intensity based on molecular subtype.^{22,34-36)}

3. Leukemias

Although leukemia is a blood-based cancer, it exploits angiogenesis in the bone marrow microenvironment. Studies have shown increased microvessel density and elevated levels of angiogenic factors, such as VEGF and

bFGF, in children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), which often decline after chemotherapy. Leukemic cells stimulate marrow endothelial cells, while the hypoxic marrow niche stabilizes HIF-1 α , promoting VEGF production and the formation of sinusoidal vessels that support leukemia growth. Although the prognostic value of marrow angiogenesis in ALL is inconsistent, higher angiogenic activity has been linked to aggressive AML and high-risk ALL. Some forms, such as Down syndrome ALL, show unique angiogenic and cytokine profiles.³⁷⁻⁴² Although direct antiangiogenic therapies are not yet standard, early trials with drugs such as thalidomide, lenalidomide, and sorafenib (a VEGFR inhibitor) have shown limited but promising results. New strategies aim to disrupt the leukemia-supportive niche by targeting pathways such as CXCR4/stromal cell-derived factor 1 (SDF-1) and HIF-1 α , thereby impairing vascular support. Although angiogenic markers are not routinely used in leukemia care, they have the potential to monitor treatment responses and guide future therapies. Ongoing research suggests that targeting the vascular niche may enhance leukemia control, particularly in cases of residual disease.^{39,40}

4. Pediatric sarcomas (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma)

Angiogenesis plays a key role in pediatric sarcomas, particularly osteosarcoma, Ewing sarcoma (EWS), and rhabdomyosarcoma, all of which often spread to the lungs via the bloodstream. Osteosarcomas commonly overexpress VEGF, which correlates with advanced disease, a poor chemotherapy response, and worse survival outcomes. EWS, driven partly by EWS-FLI1 fusion, produces VEGF and IL-8 and exhibits dense vascularization on imaging. Alveolar rhabdomyosarcoma, a high-risk subtype, expresses higher VEGF levels than embryonal types and is more metastatic.⁴³⁻⁴⁶ Antiangiogenic therapies have shown promise, and trials such as the CABONE and REGOBONE have demonstrated that cabozantinib and regorafenib, both VEGFR-targeting TKIs, extend disease control in relapsed osteosarcoma and EWS. Combination regimens such as bevacizumab with sorafenib and cyclophosphamide have achieved stable disease in the majority of heavily pretreated patients with manageable toxicity. New agents such as apatinib and anlotinib, as well as dual-pathway approaches targeting VEGF and DLL4, are being explored.

Sarcomas can activate alternative angiogenic pathways when VEGF is blocked, prompting interest in multitarget strategies.^{47,48} Trials such as the PAZNTIS aim to inhibit both angiogenesis and tumor metabolism. Although antiangiogenic therapy is not curative, it is increasingly

effective in extending disease control in refractory sarcomas.^{22,43,49} Caution is needed in pediatric patients because of the risks to bone growth and wound healing; for example, bevacizumab has been linked to postsurgical complications in osteosarcoma. Despite these concerns, antiangiogenic therapy has become a crucial component of sarcoma management, laying the groundwork for more comprehensive and personalized treatment approaches.⁵⁰

Clinical significance of angiogenesis markers

Angiogenesis-related biomarkers play a pivotal role in our understanding of pediatric cancer biology and hold promise for guiding therapy. Elevated levels of proangiogenic factors such as VEGF are generally associated with worse outcomes as demonstrated in osteosarcoma and NB, in which markers like VEGF and HIF-1 α are correlated with a poor prognosis and advanced disease. Despite some context-dependent findings such as higher VEGF levels in differentiated NB with favorable outcomes, the consensus remains that aggressive tumors exhibit heightened angiogenic activity. In MB, markers such as VEGF and CD105 aid the risk stratification. In patients with ALL, changes in angiogenic cytokines during treatment may indicate a disease response or the presence of minimal residual disease.^{30,35,42,51}

Angiogenic markers also have potential for diagnostics and monitoring. Techniques such as dynamic contrast-enhanced magnetic resonance imaging and perfusion computed tomography noninvasively assess tumor perfusion and circulating biomarkers such as plasma VEGF or Ang-2 are being investigated for the early detection of relapse. VEGF-D, which is associated with lymphangiogenesis, may further improve our understanding of the metastatic potential of specific cancers. Although these tools are primarily used in the research phase, they may support early intervention strategies. Angiogenic markers have emerging theranostic value. The expression profiles of VEGF, PDGF, and other angiogenic genes may inform antiangiogenic therapies or clinical trials. Simultaneously, radiolabeled agents such as bevacizumab enable functional imaging and target validation.

Moreover, angiogenic markers often intersect with other cancer hallmarks—such as HIF-1 α 's role in metabolism—offering opportunities for combination therapy. For instance, group 3 MB with c-MYC amplification and high VEGF expression represents a highly aggressive subgroup that may benefit from targeted approaches that inhibit angiogenesis. As research advances, multiparametric models incorporating angiogenic profiles are becoming increasingly viable for risk assessments and personalized

treatment. However, angiogenesis research is challenged by the lack of simple, standardized measurement models. Methods such as microvessel density, vessel co-option, pericyte coverage, and tip cell analysis have limitations and accurate interpretation depends on a nuanced understanding of tumor-specific vascular dynamics. Ultimately, integrating angiogenesis markers into clinical decision-making requires both technological refinement and a deeper understanding of the underlying biology.^{22,50,52-54)}

Therapeutic targeting of angiogenesis: recent advances

Therapeutic antiangiogenesis therapy in pediatric oncology has led to significant advancements in various strategies. Monoclonal antibodies such as bevacizumab (anti-VEGF-A) have demonstrated efficacy primarily in relapsed settings, notably in MB (MEMMAT regimen) and PLGG. Other antibodies, such as ramucirumab (anti-VEGFR-2), have limited pediatric applications, although emerging bispecific antibodies targeting VEGF and DLL4/Notch show promise despite safety concerns that require careful management.^{28,34,35,36,55)}

TKIs, including cabozantinib, regorafenib, pazopanib, sorafenib, sunitinib, and axitinib, target multiple pathways including the VEGFR pathway. TKIs have demonstrated efficacy, particularly pazopanib for pediatric refractory rhabdomyosarcoma and sunitinib for NB. However, adaptive resistance commonly develops through the upregulation of alternative angiogenic ligands (e.g., FGF and Ang-2) in tumors. Combining TKIs with other inhibitors (e.g., VEGFR and FGF receptor [FGFR] inhibitors) or monoclonal antibodies to mitigate resistance has been increasingly explored.^{22,28)}

Metronomic chemotherapy utilizes low-dose continuous regimens with antiangiogenic effects by targeting endothelial cells and inhibiting vascular repair. The MEMMAT regimen exemplifies this approach by combining chemotherapy with angiogenic inhibitors. Pediatric trials indicated that metronomic therapy induces prolonged disease stability with reduced acute toxicity, although integrating it early into treatment to prevent metastatic angiogenesis remains challenging.^{22,34)}

Antiangiogenic strategies also synergize with immunotherapy by normalizing the tumor vasculature, thereby improving immune cell infiltration. The combination of checkpoint inhibitors and angiogenesis inhibitors that have already been approved for use in adult cancers is being explored in pediatric oncology. Additionally, agents such as lenalidomide possess dual antiangiogenic and immunomodulatory effects that may enhance therapeutic

outcomes as suggested by preliminary pediatric studies.^{5,22,29)}

Finally, targeting angiogenesis beyond the VEGF pathway includes inhibiting IL-8 signaling via CXCR2 inhibitors, disrupting vessel maturation with TIE2 kinase inhibitors or Ang-2 antibodies, and inhibiting endothelial cell glycolysis (e.g., using PFKFB3 inhibitors such as 3PO). These novel strategies may overcome limitations associated with traditional VEGF-focused therapies.³⁰⁾

Mechanisms of resistance to antiangiogenic agents

A multifactorial interplay between tumor cell plasticity, microenvironmental adaptation, and compensatory vascular mechanisms drives resistance to antiangiogenic therapy in pediatric cancers.^{56,57)} A key trigger of resistance is therapy-induced hypoxia, which stabilizes HIF-1 α , leading to the upregulation of alternative proangiogenic pathways. Tumors commonly respond to VEGF inhibition by increasing the expressions of other angiogenic mediators including FGF2, PDGF, placenta growth factor (PlGF), Ang-2, and CXCL12/SDF-1, thereby restoring neovascularization via VEGF-independent routes. These changes are particularly evident in NB and other solid pediatric tumors.^{58,59)} The alternative pathways in various tumors may differ significantly. Therefore, accurate knowledge of the alternative pathways in each tumor is essential to preventing resistance to anti-angiogenesis drugs.^{56,60)}

The tumor microenvironment also plays a critical role; anti-VEGF treatment enhances the recruitment of myeloid-derived suppressor cells, TAM, and proangiogenic fibroblasts, all of which contribute to immune evasion and vessel stabilization.^{58,59,61)} In some cases, prolonged antiangiogenic pressure promotes vessel maturation via increased pericyte coverage, thus reducing therapeutic responsiveness. Structural adaptations further complicate treatment. Tumors may evade VEGF dependence by hijacking the preexisting vasculature (vessel co-option) or forming vessel-like networks without endothelial cells (vasculogenic mimicry), both of which have been observed in pediatric brain tumors, sarcomas, and melanomas.^{17,62-65)} Moreover, hypoxia-induced metabolic reprogramming, including increased glycolysis, autophagy, and lactate recycling, supports tumor cell survival under vascular stress. These mechanisms often co-occur, as exemplified in NB, in which VEGF blockade induces HIF-1 activation, alternative angiogenic signaling, immune suppression, and metabolic adaptation. Taken together, these insights underscore the limited durability of antiangiogenic monotherapies and highlight the need for combinatorial

strategies. Targeting multiple axes—such as the VEGF plus FGF or Ang-2 pathways or concurrently modulating the immune and stromal compartments—may enhance efficacy and delay resistance. A deeper understanding of tumor-specific angiogenic and adaptive profiles is essential for the rational design of next-generation antiangiogenic regimens in pediatric oncology.^{59,66,67)}

Strategies to overcome resistance to antiangiogenic therapy

Multiple strategies have emerged to overcome or delay resistance to antiangiogenic therapies in pediatric cancers, reflecting an evolving understanding of tumor vascular biology and resistance mechanisms. These strategies include the use of combination regimens targeting parallel pathways, the identification of predictive biomarkers for patient stratification, and the use of dosing strategies that aim to normalize rather than eradicate it.⁶³⁾

Combination therapies targeting multiple pathways

Given the plasticity of the tumor vasculature and the activation of alternative proangiogenic pathways under VEGF blockade, combination strategies represent a rational approach to enhancing efficacy and delaying resistance. Preclinical models have shown that dual inhibition, such as the VEGF and Ang-2 blockade, results in more sustained anti-tumor effects than monotherapy. Similarly, the cotargeting of VEGF and FGF signaling, both of which are upregulated under hypoxic conditions, is under investigation in early-phase trials, with potential pediatric applications. In clinical pediatric oncology, most studies have combined antiangiogenic agents with chemotherapy or other targeted agents. For instance, in NB xenografts, combining bevacizumab with HIF-1 α inhibitors (e.g., topotecan or nutlin-3a) significantly enhanced tumor suppression by mitigating hypoxia-induced escape mechanisms. Clinically, bevacizumab has been tested in combination with metronomic cyclophosphamide and vinblastine in patients with refractory solid tumors as well as with irinotecan/temozolomide in brain tumors, showing partial responses or disease stabilization in subsets of patients. Nevertheless, durable responses remain elusive, highlighting the need for more comprehensive regimens.^{59,65,67)}

Emerging strategies include pairing antiangiogenic agents with immunotherapies. VEGF inhibition normalizes abnormal tumor vessels, enhances immune cell

infiltration, and alleviates immunosuppression, thereby augmenting immune checkpoint inhibitor efficacy. This approach is now the standard for certain adult cancers (e.g., renal and hepatocellular carcinomas) and is being explored in pediatric settings. Preclinical data suggest that such combinations may be particularly effective in tumors with immunosuppressive microenvironments, such as NB or osteosarcoma. Other novel combinations under investigation include antiangiogenics with c-MET inhibitors (to reduce invasion), β -integrin inhibitors (to disrupt matrix remodeling), and epigenetic modulators (to suppress the hypoxia response). Early-phase pediatric trials, such as those involving cabozantinib (a VEGFR/MET inhibitor) combined with temozolomide/irinotecan in NB or bevacizumab with mammalian target of rapamycin (mTOR) inhibitors in high-grade gliomas, have shown promising activity but require further validation.^{58,59,63)}

Biomarkers for response prediction

A major challenge in pediatric antiangiogenic therapy is the absence of validated biomarkers to predict the response or enable the early detection of resistance. Candidate circulating biomarkers include VEGF, PlGF, FGF2, Ang-2, and IL-8, whose increasing levels during therapy have been associated with tumor progression in adult studies. These findings may reflect tumor adaptation to hypoxia and could potentially serve as early indicators of therapeutic resistance. Pediatric trials are beginning to explore these correlations. For example, a Children's Oncology Group study evaluated plasma VEGF and Ang-2 levels as biomarkers in recurrent MB treated with bevacizumab.^{22,67,68)}

Genomic and transcriptomic approaches are under development. Gene expression signatures associated with FGF/FGFR pathways, HIF-1 α activity, or hypoxia response may help predict resistance and inform combinatorial strategies. Imaging-based biomarkers are also gaining traction.⁶⁷⁾ Functional magnetic resonance imaging and positron emission tomography-based modalities have demonstrated that changes in tumor perfusion or diffusion can correlate with a response to antiangiogenic therapy. In pediatric brain tumors, apparent diffusion coefficient values have been proposed as potential predictors of the response to bevacizumab. However, no single biomarker has demonstrated sufficient reliability or reproducibility, and a composite panel integrating clinical, molecular, and imaging data may be required. Ongoing collaborative efforts, such as the MAGIC consortium, are working to identify and validate predictive markers through systematic biospecimen collection in clinical

Dosing and schedule modifications

Traditional antiangiogenic dosing regimens aim to maximize vessel suppression; however, recent insights suggest that lower sustained dosing may offer superior outcomes by promoting vascular normalization. The vascular normalization hypothesis, pioneered by Jain, posits that judicious antiangiogenic dosing can transiently restore tumor blood vessel structure and function, improving drug delivery and oxygenation while minimizing hypoxia-driven resistance. Preclinical studies have shown that high-dose, short-duration therapy can paradoxically worsen hypoxia and drive tumor invasiveness, whereas metronomic dosing prunes aberrant vessels without inducing severe hypoxia. Pediatric trials have adopted metronomic schedules such as daily low-dose oral cyclophosphamide with intermittent bevacizumab to reduce rebound angiogenesis. Adaptive scheduling is another promising strategy in which antiangiogenic therapy is administered in a sequence that optimizes its synergistic effects with chemotherapy or radiation. For example, in NB models, delivering bevacizumab a few days before chemotherapy enhances drug penetration and tumor control. Moreover, perioperative management protocols for pediatric sarcomas recommend halting antiangiogenic agents (e.g., bevacizumab) for several weeks before surgery to avoid wound healing complications. Although dose and schedule adjustments alone are unlikely to eliminate resistance, they can meaningfully extend the treatment benefits and improve the therapeutic index. These findings emphasize that antiangiogenic therapy must be carefully timed and dosed to avoid inadvertently fostering the exact resistance mechanisms it seeks to overcome.⁵⁸⁾

Novel agents and targets

Overcoming resistance to antiangiogenic therapy in pediatric cancers may require novel agents that target distinct mechanisms beyond the traditional VEGF pathways. Several innovative approaches were recently developed. For example, HIF-2 α inhibitors (e.g., belzutifan), which are effective treatments against hypoxia-driven adult tumors, could potentially interrupt hypoxia-mediated angiogenic escape mechanisms in pediatric cancers, particularly when combined with VEGF inhibitors.⁵⁸⁾ Targeting endoglin (CD105), an endothelial-specific TGF- β receptor upregulated in angiogenic vessels, has also shown

promise. The antibody carotuximab (TRC105), tested in preclinical NB models, selectively eliminated endoglin-expressing endothelial cells, enhancing tumor regression when combined with immunotherapy.⁵⁸⁾ Similarly, inhibiting Bv8/PROK2 signaling, which drives myeloid cell-dependent angiogenesis, represents another potential immunomodulatory antiangiogenic approach demonstrated in animal studies but not yet clinically evaluated in children.⁵⁹⁾ CXCR4 antagonists such as plerixafor disrupt SDF-1-mediated recruitment of proangiogenic myeloid progenitors, thereby augmenting anti-VEGF effects and providing rationale for clinical exploration in resistant pediatric solid tumors.⁵⁹⁾

Inhibitors targeting the angiopoietin/Tie2 axis (e.g., trebananib) have also shown early clinical safety in pediatric trials, with preclinical studies indicating potential synergy when combined with VEGF blockade.^{58,59)} New multitarget TKIs (e.g., lenvatinib, which targets VEGFR, FGFR, PDGFR, and KIT) may prevent resistance by broadly inhibiting angiogenic signals. Lenvatinib combined with everolimus (an mTOR inhibitor) has been investigated in treatment-refractory pediatric solid tumors. Bispecific antibodies that simultaneously neutralize the VEGF and DLL4/Notch pathways to counteract compensatory angiogenesis are under development.⁵⁸⁾ Clinically, the CABONE trial highlighted the efficacy of cabozantinib in pediatric osteosarcoma, suggesting that dual targeting of VEGFR2- and MET-mediated invasion can effectively circumvent resistance after VEGF blockade failure. Similarly, pazopanib combined with metronomic chemotherapy improved progression-free survival in pediatric sarcomas, underscoring the advantage of simultaneously targeting endothelial and tumor cells. Overall, the evolution toward personalized, biomarker-informed, and strategically combined therapies is essential since it proactively anticipates and mitigates resistance in pediatric oncology.⁵⁸⁾

Summary and future directions

Antiangiogenic therapies are integral to pediatric oncology but limited by the rapid development of resistance. Pediatric tumors evade treatment through alternative angiogenic pathways (FGF, PDGF, and Ang-2), microenvironmental support, hypoxia-driven HIF-1 signaling, metabolic reprogramming, and structural adaptations such as vascular co-option. Although the responses to bevacizumab and TKIs are often transient, these resistance mechanisms present actionable targets for further investigation. Future strategies should focus on rational combinations such as anti-VEGF agents with checkpoint

inhibitors, hypoxia modulators, or stromal-targeting drugs guided by biomarkers, including gene signatures or perfusion imaging. Personalized adaptive approaches incorporating innovative dosing (e.g., chronotherapy) and novel agents targeting vessel mimicry or endothelial antigens hold promise for overcoming resistance and improving outcomes.^{58,71,72)}

Guidelines for using antiangiogenic agents in pediatric malignancies

This guidelines-based approach (Fig. 1) provides practical recommendations for incorporating antiangiogenic therapy in pediatric malignancies and is particularly valuable in resource-limited settings. In centers capable of assessing tumor-specific angiogenic profiles, selective targeting with antiangiogenic therapies is recommended. Additionally, combining low-dose weekly chemotherapy (e.g., vinblastine 3 mg/m²) with oral antiangiogenic agents (e.g., valproic acid and celecoxib) may effectively inhibit tumor progression, especially during the critical early phase of metastatic spread.

Conclusion

In summary, personalized medicine has the potential to support the angiogenic mechanisms employed by tumors.

Personalized antiangiogenic therapy should integrate the knowledge of tumor-specific vascularization and metabolism with biomarker-guided treatment strategies. Along with new drug development, efforts must focus on discovering reliable markers of pathway activation and response. Existing evidence supports the combination of angiogenesis inhibitors with chemotherapy in many solid tumors; however, finer patient selection and treatment timing will likely improve outcomes. Finally, agent duration and scheduling remain open questions. The current practice of continuous therapy is empirical, and clinical trials are needed to define the most effective and safe protocols. By addressing these challenges, antiangiogenic treatment can be optimized as part of a precise oncology strategy that provides better predictions of benefits and reduces the risk of resistance in pediatric malignancies. In addition to conventional or salvage chemotherapy, antiangiogenic agents can be adjunctive chemotherapy medications, especially for solid tumors.

Footnotes

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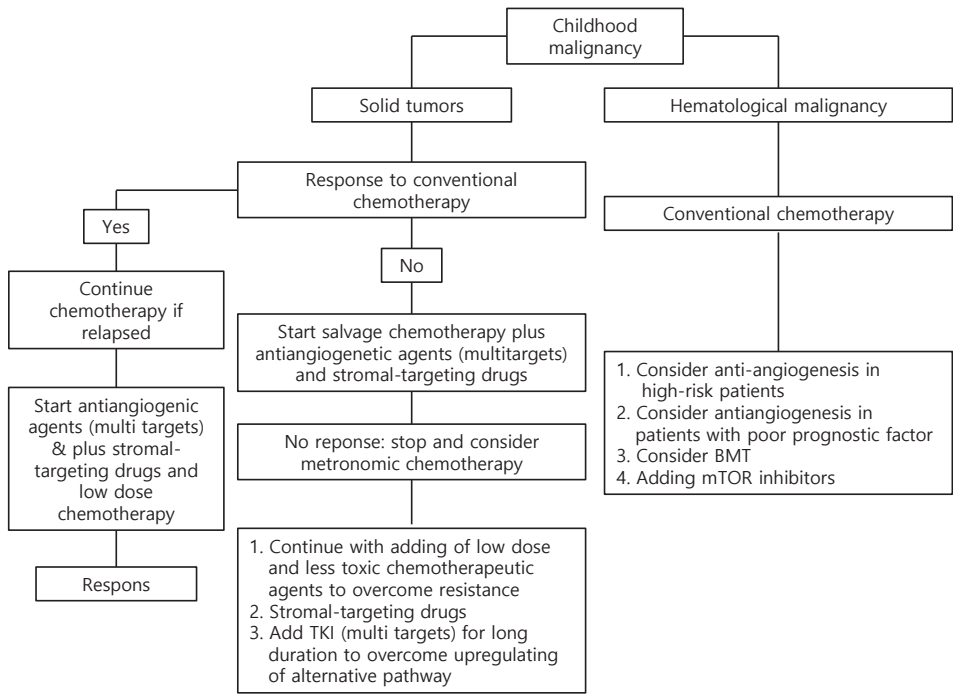


Fig. 1. Guidelines-based approaches to antiangiogenesis therapy in pediatric malignancy in countries with limited resources. BMT, bone marrow transplantation; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

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