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Overcoming Anti-Angiogenic Resistance in Pediatric Sarcomas

Nader Shakibazad, M.D.
Associate Professor of Pediatric Hematology and Oncology
Bushehr University of Medical Sciences, Bushehr, Iran

Email: ***nshakibazad@gmail.com***

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- Acknowledgment to collaborating institutions and ongoing research in pediatric oncology and angiogenesis.”

Agenda

- Angiogenesis in pediatric sarcomas
- Mechanisms of resistance
- Biomarkers that guide action
- Therapeutic option to overcome resistance
- Simple, effective combo protocol example
- Q&A / key take-homes

Angiogenesis in Pediatric Sarcomas
Background

- Pediatric sarcomas (e.g. OS, ES, RMS) are highly **angiogenesis-dependent**
- **AAT** (VEGF antibodies like bevacizumab, VEGFR tyrosine kinase inhibitors like sorafenib) aim to **starve the tumor** by cutting off its blood supply.
- VEGF inhibitors can delay tumor growth or cause **transient** stabilization in sarcomas.
- **Problem:** Benefits are **modest and short-lived**
- Need to overcome a variety of **compensatory mechanisms** that **sarcomas** use to escape VEGF blockade.

The Resistance Problem
Transient Responses

- **Short-lived efficacy:** VEGF inhibitors **no sustained shrinkage** in pediatric sarcomas. Tumor control is usually transient.
- **Inevitable resistance:** Virtually all tumors eventually progress on anti-angiogenic therapy – resistance may be **primary** (no initial response) or **acquired** (tumor relapses after initial benefit).
- Tumors restore their blood supply via **alternate pathways, microenvironment changes, or hypoxia-driven adaptations**, leading to renewed growth despite VEGF blockade.
- Paradoxically, VEGF-targeted treatment creates a **hypoxic environment** that **pressures the tumor to evolve** new survival tactics.

Resistance Mechanism 1
Alternate Angiogenic Pathways

- **Pathway switching:** When VEGF is blocked, tumor and stromal cells crank up other **pro-angiogenic** factors **(FGF, PDGF-BB, Ang-2, HGF**, etc.) to bypass the VEGF pathway.
- Pediatric **OS** often **have high baseline FGF/PDGF** expression, indicating these alternate pathways drive angiogenesis and tumor aggressiveness.
- **Angiopoietin-2 (Ang-2)** tends to rise **after anti-VEGF therapy** and correlates with resistance.
- A **redundant network** of angiogenic signals. Even if VEGF is neutralized, alternate growth factors keep blood vessels growing.
- **Monotherapy against VEGF yields only transient benefit as the tumor "reroutes" through other angiogenic circuits.**

Resistance Mechanism 2
Vascular Co-Option

- **Co-option:** Tumor cells hijack existing normal blood vessels in nearby tissue instead of growing new ones.
- These **co-opted vessels** provide nutrients and oxygen without requiring any VEGF-driven angiogenesis.
- Tumors relying on **co-option (seen in some OS with lung metastases)** are often intrinsically **insensitive to VEGF inhibitors** –
- Anti-VEGF therapy can even **increase vessel co-option** as an adaptive response
- Bottom line: **Co-option allows continuous tumor perfusion** even when angiogenesis is blocked, undermining the efficacy of VEGF-targeted drugs.
- Some sarcomas simply **(co-option)** – since they don't need to form new vessels, VEGF inhibitors can't starve them.

Resistance Mechanism 3
Vasculogenic Mimicry

- **Tumor-built channels:** In vasculogenic mimicry, tumor cells themselves form vessel-like channels that carry blood, **without any endothelial cells**. **“pseudo-vessels”**
- Aggressive sarcomas can partially transform to an endothelial-like state and organize into tube networks lined entirely by tumor cells.
- These tumor-cell channels create an **alternative microcirculation** that supplies the tumor. Crucially, vasculogenic mimicry does **not depend on VEGF or normal vessels**, so VEGF/VEGFR inhibitors do not stop it.
- Anti-angiogenic therapy can **promote vasculogenic mimicry**. Tumors increased their mimicry channels after bevacizumab treatment or under prolonged low-oxygen conditions.
- Vasculogenic mimicry correlates with **poor outcomes** in sarcomas (and other cancers). It signifies an aggressive tumor phenotype. Currently, no standard therapies directly target mimicry

Resistance Mechanism 4
Microenvironment Support (Pericytes & Myeloid Cells)

- **Pericyte protection:** Under VEGF blockade, the tumor's remaining blood vessels become more heavily coated with **pericytes** (support cells that wrap vessels). **These pericyte-rich vessels are resistant to pruning by VEGF inhibitors**.
- Mechanism: VEGF inhibition often **upregulates PDGF-B/PDGFR-β signaling**, which recruits pericytes to vessels. This explains why adding PDGFR inhibitors can help – to prevent pericyte-driven vascular "rescue."
- **Myeloid cell influx:** Anti-angiogenic therapy-induced **hypoxia** triggers release of **chemokines** (e.g. SDF-1/CXCL12) that **recruit bone marrow–derived myeloid cells** (MDSCs, macrophages) into the tumor.
- These infiltrating cells are highly pro-angiogenic: they secrete VEGF, FGF2, **Bv8** (Prokineticin-2), matrix metalloproteinases, and other factors that **reactivate blood vessel growth** or even form vessel-like structures.
- Clinically, tumors that become resistant to bevacizumab often show high MDSC infiltration. Elevated circulating neutrophils or a **high neutrophil-to-lymphocyte** ratio (reflecting many myeloid cells) is a **biomarker of poor response** to VEGF inhibitors.

Resistance Mechanism 5
Cancer-Associated Fibroblasts (CAFs)

- **Fibroblast "angiogenic switchboard":** CAFs in the tumor stroma activate and secrete many **pro-angiogenic factors**. They can produce VEGF themselves and other growth factors (**FGF2, HGF, PDGF-C**, etc.) that sustain angiogenesis even if the tumor cells' VEGF is blocked.
- In models of resistance, **CAFs from resistant tumors** express higher levels of angiogenesis genes (e.g. **PDGF-C, Angptl2**) than CAFs from sensitive tumors. These **resistant CAFs** promote tumor **vascularization** despite VEGF blockade.
- **CAFs** also remodel the tumor matrix and secrete chemokines (like **SDF-1**) to **recruit endothelial progenitor cells and more myeloid cells into the tumor**.
- **Microenvironmental rescue:** Under therapy pressure, the tumor "co-opts" its microenvironment: increased pericyte protection, influx of pro-angiogenic myeloid cells, and fibroblast-derived factors collectively **maintain blood vessels via alternate means**. This is why **multi-target approaches are needed**

Resistance Mechanism 6
Hypoxia & HIF-Driven Adaptations

- **Therapy-induced hypoxia:** Anti-angiogenic treatment prunes tumor vessels, causing low oxygen regions. Hypoxia stabilizes **HIF-1α/HIF-2α** transcription factors, which turn on broad survival programs.
- **Rebound angiogenesis:** HIF-1α strongly upregulates VEGF (and other angiogenic factors). As a result, vessel pruning leads to a **surge of VEGF production**, driving new vessel growth despite therapy.
- **Metabolic shift:** HIF activation pushes cancer cells into glycolysis and autophagy to adapt to low oxygen. Tumors switch from aerobic metabolism to **anaerobic glycolysis**, upregulating glucose transporters and enzymes to **generate ATP without oxygen**. They also induce autophagy (self-cannibalization for energy) to survive nutrient deprivation. These metabolic tweaks make tumor cells **less dependent on blood supply**, undermining the “starvation” strategy.
- **Immune escape:** Hypoxia triggers an **immunosuppressive t**umor milieu. HIF-1α increases **PD-L1** on tumor cells, which **switches off T-cells.** Low oxygen also attracts regulatory T-cells and **MDSCs/M2 macrophages**, and promotes release of cytokines (IL-10, TGF-β) that dampen immunity. The result is a tumor that is harder for the immune system to attack under prolonged anti-angiogenic therapy.
- **Invasiveness:** HIF-driven changes can make tumors more aggressive. Hypoxia can induce **epithelial-to-mesenchymal transition (EMT)**, increasing cancer cell motility and invasiveness. In some models, while anti-angiogenic drugs slowed primary tumor growth, they paradoxically led to **more invasion and metastasis**, partly due to **HIF-induced EMT and migration**.

Why Multi-Modal Strategies?

- **No single silver bullet:** The myriad resistance mechanisms (alternative growth factors, vessel co-option, stromal support, hypoxia adaptations) make it clear that **blocking one pathway (like VEGF) is not enough**.
- Tumors are highly adaptable – when one route is blocked, they **re-route through others or change behavior**. For example, **VEGF inhibition** may simply drive the tumor to use **FGF/PDGF** or to become more invasive and hypoxic.
- **Multi-modal approach:** To improve outcomes, we need to tackle resistance on multiple fronts simultaneously. Researchers are exploring **combination therapies**, **microenvironment modulation**, **adaptive treatment adjustments**, **and innovative dosing** to counter tumor feedback.
- This means **hitting multiple targets at once**, anticipating tumor escape routes, and personalizing treatment to tumor biology. By addressing each key resistance mechanism (pathways, immune evasion, hypoxia, etc.), we aim to achieve more durable control.
- **Key strategies overview: Combine VEGF inhibitors with other pathway blockers**; **add immunotherapy**; **target support cells (pericytes, macrophages, CAFs**); use **biomarkers to adapt therapy** in real time; and **optimize dosing (metronomic, timed dosing).**

Strategy 1
Multi-Target Pathway Blockade

- **Block VEGF + alternate pathways:** Use combinations to inhibit **VEGF and** other angiogenic signals (FGF, PDGF, Ang-2, HGF, etc.). By doing so, we prevent the tumor from compensating via a single alternate pathway.
- **Multi-target TKIs:** Drugs like **Pazopanib, Sorafenib, Regorafenib, Cabozantinib** hit several angiogenic receptors **at once** (VEGFR plus PDGFR, FGFR, MET, etc.). In refractory sarcomas, these broad-spectrum TKIs have achieved improved disease stabilization compared to single-target agents. They essentially "cast a wider net" so the tumor has fewer escape options.
- **Example – Cabozantinib:** A multi-kinase inhibitor targeting VEGFR2 and MET (HGF receptor). In **relapsed OS**, Cabozantinib significantly prolonged progression-free survival by **simultaneously blocking VEGF and HGF/MET pathways**, outperforming historical outcomes. This illustrates how multi-pathway targeting can translate to tangible patient benefit

Strategy 2
Anti-Angiogenic + Immunotherapy

- **Dual approach: Pair VEGF/VEGFR inhibitors** with **immune checkpoint inhibitors** (ICIs, e.g. anti-PD-1/PD-L1). This addresses two resistance facets: abnormal vasculature/hypoxia and tumor immune evasion.
- **ICIs activate immune attack:** Meanwhile, ICIs (like pembrolizumab, nivolumab) reactivate T-cells to recognize and kill cancer cells, countering the hypoxia-induced immunosuppressive environmental **synergistic combination with anti VEGF**
- **Proven synergy:** In adults, VEGF+ICI combos have improved outcomes and gained approvals (e.g. **bevacizumab + atezolizumab** in liver cancer significantly improved survival vs either alone; **axitinib + pembrolizumab** in kidney cancer, etc.). These successes validate the concept that **starving the tumor and attacking it with the immune system simultaneously** yields better results.
- **Pediatric trials:** Now being tested in sarcomas. Example: SARC032 trial of **regorafenib (VEGFR TKI) + pembrolizumab** in OS is ongoing. Early case reports are encouraging – e.g., a few refractory osteosarcoma patients had **dramatic, durable responses** on **nivolumab + Cabozantinib** (PD-1 blocker + VEGFR/MET inhibitor). These are small numbers, but they hint that the **VEGF+immunotherapy** synergy may translate to pediatric tumors as well.

Strategy 3
Targeting Stromal Support: Pericytes & Myeloid Cells

- **Hit the pericytes:** Add **PDGFR inhibitors** (e.g. imatinib, sunitinib) alongside VEGF inhibitors to disrupt pericyte attachment to tumor vessels. By blocking PDGFR-β signaling, we **prevent pericytes from shielding blood vessels**, making those vessels easier to destroy.
- **Preclinical proof:** In mouse models, combining a PDGFR blocker with anti-VEGF led to much more effective tumor vessel regression and suppression of growth than either alone. In some cases, **adding a PDGFR inhibitor yielded complete tumor responses** whereas VEGF inhibitor alone could not. This confirms that removing pericyte support can dramatically enhance anti-angiogenic therapy.
- Notably, **multi-target TKIs like Cabozantinib and sunitinib already** hit PDGFR in addition to VEGFR – this may explain their success in some refractory sarcomas, since they inherently **prevent pericyte-mediated rescue** of vessels.
- **Block myeloid cell recruitment:** Target the **SDF-1/CXCR4 axis** that summons bone marrow-derived cells after VEGF therapy. A CXCR4 inhibitor (plerixafor) can block MDSCs from homing to the tumor, thereby **reducing the influx of pro-angiogenic immune cells**.
- **Evidence:** In resistant tumor models, CXCR4 blockade after anti-VEGF treatment led to fewer MDSCs in tumors and improved anti-angiogenic efficacy.
- **Other immune targets**: Inhibiting **CSF-1R** can deplete tumor-associated macrophages, and neutralizing **Bv8** (a neutrophil/MDSC-derived angiogenic factor) can prevent rebound vessel growth. Combining anti-VEGF with an **anti-Bv8 antibody** delayed or prevented angiogenic escape in animal studies.

Strategy 4
Targeting Cancer-Associated Fibroblasts (CAFs)

- **Cut off fibroblast signals: Neutralize CAF-derived factors** that promote angiogenesis. Adding an **FGF inhibitor or PDGF-C neutralizing antibody** can shut down that alternate pathway.
- **Example:** combining an **FGF2-neutralizing antibody** with **sorafenib** (a VEGFR/PDGFR inhibitor) had additive anti-tumor and anti-angiogenic effects. By blocking CAF-derived FGF, they **overcame resistance** to VEGF inhibition.
- **Deplete CAFs:** Another tactic is to remove the fibroblasts altogether. Drugs targeting **Fibroblast Activation Protein (FAP)**, a cell-surface protein on many CAFs, are in development to selectively kill or reduce CAFs.
- **Multi-component combos:** Real-world application may involve **triplet regimens** – e.g., VEGF inhibitor + a CAF-targeted agent + another therapy (chemotherapy or immunotherapy) – to attack multiple resistance mechanisms simultaneously.
- **Caution:** The challenge is achieving this **without undue toxicity**, since pathways like FGF, PDGF, etc., also play roles in normal physiology. However, preclinical evidence strongly supports that **multi-targeting the "soil" (microenvironment) along with the tumor** is key to preventing angiogenic escape.

Strategy 5
Biomarker-Guided Adaptive Therapy

- **Real-time monitoring:** Track **circulating angiogenic factors** in the blood (**VEGF, FGF2, Ang-2, VEGF-C**, etc.) during treatment. If we see certain factors rising, it can signal that the tumor is escaping via those pathways.
- *Example:* An increase in **Angiopoietin-2 (Ang-2)** levels during bevacizumab therapy is associated with poor outcome (tumor switching to Ang-2-driven angiogenesis).
- **Adapting therapy:** If Ang-2 starts climbing, add an Ang-2 inhibitor (or switch to a drug that targets Ang-2/Tie2) to cut off that escape route. Similarly, a spike in FGF or PDGF during VEGF blockade could prompt adding an FGF or PDGFR inhibitor.
- **Adaptive combinations:** This approach means treatment is not static. **We can dynamically add or switch drugs based on biomarker changes**. The tumor "declares" which pathway it's using to resist (through rising factor levels), and we respond in real time with a tailored countermeasure. Essentially, therapy evolves as the tumor evolves.

Strategy 5
Biomarker-Guided Adaptive Therapy

- **Molecular profiling:** Use the tumor's gene expression or protein signature to guide initial combo choice. For example, a sarcoma with a "high hypoxia/VEGF" gene signature might benefit from starting with a multi-target TKI (or adding a HIF inhibitor), whereas an "immune-rich" tumor profile might prompt adding immunotherapy early. We can also stratify patients by baseline blood biomarkers: a tumor with extremely high FGF or Ang-2 at baseline might be flagged as needing upfront combination (VEGF + FGF inhibitor), since it's likely to resist VEGF-alone therapy.
- **Personalized & proactive:** This biomarker-driven strategy **personalizes treatment in real time**. Instead of waiting for the tumor to visibly progress, we adjust the regimen when molecular signs of resistance appear. This could **prevent full-blown resistance** by catching it early.
- ***Illustration:*** In one clinical study, rising plasma **Ang-2** predicted bevacizumab failure; theoretically, by adding an Ang-2 blocker at that point, one might rescue the anti-angiogenic effect. Trials are beginning to test such adaptive protocols.

Strategy 6
Optimized Dosing: Metronomic & Chronotherapy

- **Metronomic therapy:** Use **continuous low-dose (metronomic) chemotherapy or targeted therapy** rather than big intermittent doses. This keeps constant pressure on tumor vasculature, preventing the regrowth spurts that can happen during drug "breaks".
- Metronomic dosing **promotes vessel normalization and reduces severe hypoxia**, which can curb the tumor's ability to mount a resistance response. It also tends to be less toxic and can stimulate the immune system (some low-dose chemo regimens boost anti-tumor immunity).
- *Example:* Metronomic **oral cyclophosphamide** (daily low-dose) has shown prolonged disease stabilization in some sarcoma maintenance therapy settings. By **continuously** suppressing angiogenesis, it prevented the tumor from rebounding between cycles.
- **Chronotherapy:** Align drug administration with the body's **circadian rhythm**. The efficacy and toxicity of anti-cancer drugs can vary based on timing (day vs night). Giving treatment at those optimal times could **maximize impact on tumor vessels and minimize side effects**.
- **Reduced resistance:** Metronomic schedules avoid the on/off effect that can lead to **rebound angiogenesis** (when drug levels drop, tumors often surge VEGF). **Constant low dosing starves the tumor more steadily** and denies it the chance to recover. Chronotherapy might reduce toxicity-related breaks, helping maintain consistent dosing. Both strategies aim to **keep anti-angiogenic pressure continuously high** without tipping into intolerable toxicity.

Strategy 7
Personalized Therapy Using Predictive Biomarkers

- **Not all sarcomas are equal:** Resistance mechanisms differ per patient.
- Predictive biomarkers can help identify which tumors will respond to anti-angiogenic therapy and which won't. This guides who should get certain drugs or combos from the start.
- **Baseline angiogenic profile:** For example, a tumor with **high VEGF-A or Placental Growth Factor (PlGF)** levels might be highly "VEGF-driven" and thus initially very responsive to VEGF blockade. In contrast, a tumor with extremely high baseline **FGF2 or Ang-2** might be primed to escape via those pathways, suggesting it could be **intrinsically resistant** to VEGF-only therapy. Such a patient might benefit from upfront combination (VEGF + FGF inhibitor, for instance) rather than VEGF monotherapy.
- **Genomic and gene expression markers:** Tumor gene signatures can categorize sarcomas by angiogenesis vs immune status. A tumor with a **"high angiogenesis" gene signature** (lots of VEGF/VEGFR/HIF target genes) is a good candidate for anti-angiogenic drugs. A tumor with an **"immune-infiltrate" signature** might do better with immunotherapy in the mix. If a sarcoma shows a strong **hypoxia/HIF gene signature**, that hints it may quickly develop angiogenic escape – perhaps consider adding a HIF-2α inhibitor or metabolic modulator upfront.

Strategy 7
Personalized Therapy Using Predictive Biomarkers

- **Blood-based predictors:** As noted, a high **Neutrophil: Lymphocyte Ratio (NLR)** (reflecting many myeloid cells) correlates with poor bevacizumab outcomes. Similarly, high circulating **VEGF-C** might predict a tumor ready to switch to lymphangiogenesis (making lymphatic vessels) as a resistance route. These kinds of biomarkers could tell us *who* is likely to benefit from anti-angiogenic therapy and who might need alternative or additional treatments.
- **Integrated approach:** The future is combining multiple types of biomarkers – blood factors, tumor genomics, imaging – to **tailor therapy choices** for each child. For instance, **genomic profiling** + **liquid biopsy (blood)** can be used even in pediatric cases to ensure we select the optimal drug combination and know when to switch or escalate treatment. Clinical trials are beginning to incorporate such biomarker-driven decision-making.
- **Efficiency:** Using **predictive markers** means we can avoid giving toxic drugs that a particular tumor is unlikely to respond to (sparing side effects and time), and focus on therapies that the tumor is "wired" to be sensitive to. This **maximizes efficacy while minimizing unnecessary toxicity**, a crucial balance in children
- **Take-home message: Right drug(s) for the right tumor.**

Example Combination Protocol

Gaspar N, et al. Lenvatinib with etoposide plus ifosfamide in patients with refractory or relapsed osteosarcoma (ITCC-050): a multicenter, open-label, multicohort, phase 1/2 study.

- **Real-world combo:** A recent Phase 2 trial in **relapsed osteosarcoma** combined **lenvatinib** (a multi-target VEGFR/FGFR TKI) with traditional chemotherapy (**ifosfamide + etoposide**). This regimen significantly improved disease control compared to historical outcomes with chemo alone
- **Impressive results:** At 4 months, **80% of patients were progression-free** on the lenvatinib + chemo combo (vs ~50% on prior chemo-only studies) **Median progression-free survival (PFS) extended** to ~8.7 months– roughly doubling what is expected with chemotherapy alone in this setting. Some patients achieved partial tumor responses or prolonged stable disease on the combination.
- **Rationale:** Lenvatinib targets VEGFR and other angiogenic pathways, **normalizing the tumor vasculature and starving the tumor**, which likely enhances the effectiveness of chemotherapy (better drug delivery, less hypoxia). Meanwhile, chemo (ifosfamide/etoposide) kills the cancer cells directly. The combo thus hits the tumor's blood supply and the tumor cells simultaneously.
- **Tolerability:** The combination was manageable in a multi-center setting, with side effects considered acceptable for the improved tumor control (supportive care was used to mitigate toxicity. This suggests the protocol is **accessible and could be implemented** in practice, especially since all components (lenvatinib, ifosfamide, etoposide) are commercially available.
- **Implication:** This example shows how adding an anti-angiogenic agent to standard chemotherapy can **overcome resistance and improve outcomes**.

Challenges & Future Directions

- **Managing toxicity**: A key challenge is **balancing efficacy with tolerability**.
- **Selective targeting**: **Broad inhibition can harm normal tissues**
- **Patient selection & biomarkers**: We need to refine **which patients get which combinations**.
- **Clinical trials underway**: Ongoing pediatric trials (e.g. combinations of VEGF inhibitors with immunotherapy, or VEGF + MET inhibitors, etc.) will shed light on optimal combos and **timing** (concurrent vs sequential). **Novel targets on horizon:** Research is identifying new resistance-related targets – e.g. **HIF-2α inhibitors** (to directly tackle hypoxia signaling) or drugs against **Bv8** (to block neutrophil-driven angiogenesis).
- **Collaboration**: **Multidisciplinary teamwork – oncologists, researchers, pharmacologists** – is crucial to convert these innovative strategies into **standard pediatric care** that improves survival.

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Thank you

Questions & Discussion

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Talk: Overcoming Anti-Angiogenic Resistance in Pediatric Sarcomas

Nader Shakibazad, MD
Associate Professor of Pediatric Hematology & Oncology
Bushehr University of Medical Sciences
Email: nshakibazad@gmail.com