TARGETING TUMOR ANGIOGENESIS

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Antiangiogenic Therapy for Metastatic Breast Cancer

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M etastatic breast cancer (MBC) is the second leading cause of cancer-related death among women in the US, accounting for an estimated 40,000 deaths (1-5). The overall survival times of patients with MBC and/or metastatic breast cancer deaths, improvements in survival for MBC have been relatively modest, and new therapies are needed to improve outcomes in this patient population.

Angiogenesis plays an important role in the development, tissue invasion, and metastasis of breast and other solid tumors (6). Both preclinical and clinical evidence support the role of angiogenesis in breast cancer pathogenesis. Several factors contribute to the development of mammary hyperplasia to malignancy, while in the clinical setting, markers of angiogenesis in early stage breast cancer, such as high microvessel density, have been correlated with metastasis and poor clinical outcome.

The predominant mediator of tumor angiogenesis is vascular endothelial growth factor (VEGF). The VEGF is secreted by various cell types to elicit a cascade of events that promote survival, proliferation, and migration of endothelial cells to proliferate and migrate from pre-existing vessels toward VEGF. Tumor cells produce factors that are upregulated and that are angiogenic, such as growth factors, cytokines, and chemokines, which are produced in response to hypoxia and other changes in the microenvironment. These growth factors are secreted by tumor cells and can be angiogenic, leading to the development of new blood vessels.

Clinical Evidence for Antiangiogenic Therapy for MBC

Monoclonal Antibodies
Bevacizumab (BV, Avastin®), a humanized monoclonal antibody against VEGF, has been shown to improve outcomes in patients with metastatic breast cancer. Taxanes, including both paclitaxel and docetaxel, have shown to be synergistic in vitro with antiangiogenic agents that bind and sequester circulating VEGF, and small molecule orally administered tyrosine kinase inhibitors (TKIs) that disrupt intracellular angiogenic pathways have also been studied. A phase 2 trial of BV plus docetaxel in refractory breast cancer showed an overall response rate of 41% (9.5% complete response and 31.5% partial response) (9).

Tyrosine Kinase Inhibitors
The discovery of TKIs has led to new strategies for targeting malignant angiogenesis. One such agent is sunitinib (Sutent®), a multi-targeted TKI that has shown promising results in patients with metastatic or advanced breast cancer. A recent phase 3 trial of sunitinib in patients with hormone receptor-negative disease showed an overall response rate of 48% (10). The combination of BV and sunitinib has also demonstrated activity in a phase 2 trial in refractory advanced breast cancer, with more than 6 responses observed out of 43 patients (11). Ongoing studies with this combination will assess the safety and efficacy of BV plus taxanes, antracyclines, and capcitabine in the front- and second-line MBC settings, respectively.

Safety of Antiangiogenic Therapy for MBC

Many of these agents are associated with hematologic and other toxicities. For patients with HER2-negative disease, the Combining Cisplatin and Antiangiogenic Therapy study (C9-02) compared the effect of adding BV to standard chemotherapy in patients with HER2-negative advanced breast cancer. The study showed a significant improvement in progression-free survival in the arm receiving BV compared to the control arm, with a hazard ratio of 0.75 (95% CI 0.58-0.98). The most common adverse events observed in the BV arm were fatigue, nausea, diarrhea, and mucositis.

Future Directions

Antiangiogenic therapy in breast cancer offers significant promise, and multiple ongoing studies are attempting to better define optimal treatment settings and agent selection. In the adjuvant setting, ECOG 5105 is enrolling 5,000 women to evaluate the addition of BV to standard adjuvant chemotherapy or an anthracycline-based chemotherapy. Other studies will assess the role of BV in the neoadjuvant and post-neoadjuvant settings. For patients with ER+ disease, studies suggest a association between ER status and response to endocrine therapy, and antiangiogenic agents could be used in combination with endocrine therapy to further improve outcomes. For patients with HER2-positive breast cancer, studies are ongoing to determine the role of antiangiogenic agents in the neoadjuvant, adjuvant, and metastatic settings.

References


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The CME activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint provider agreement between the Angiogenesis Foundation and the University of California, San Francisco Medical Center. The University of California, San Francisco Medical Center is accredited by the ACCME to sponsor continuing medical education for physicians. The University of California, San Francisco Medical Center designates this educational activity for a maximum of 10 AMA PRA Category 1 Credits™. It is the policy of the Angiogenesis Foundation that all individuals who have control of study content have disclosed the sources of any potential conflicts of interest. The Accreditation Council for Continuing Medical Education (ACCME) requires that all planners disclose all potential conflicts of interest. There are no relationships to disclose.

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Targeting Cells and Pathways in Advanced Breast Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels that supply tumors. Endothelial cells also provide paracrine factors to tumor cells, which in turn, release growth factors that sustain angiogenesis. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

**VEGF/other angiogenic growth factors**
- VEGF
- FGF
- EGF
- TGF-α
- TGF-β
- PDGF
- IGF-1
- Ang-1
- Ang-2

**Oxygen Delivery**
- HIF-1α
- HIF-2α

**Cell Cycle**
- CDK
- cyclin

**Cell Proliferation and Survival**
- bFGF
- EGF
- VEGF
- Her2

**Pericyte**
- Platform-derived growth factor (PDGF) and its receptor PDGFR-β mediate vessel maturation.

**Endothelial Cell**
- Vascular endothelial growth factor (VEGF) family (VEGFR-1, VEGFR-2, VEGFR-3), activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.

**Targeted Agents** (Targets shown in diagram above)
- Axitinib (AG-213736)
- Pazopanib (GW420867)
- Sunitinib (SU11248)
- Imatinib (Gleevec)
- Fotempsin (Xfad)

**Tumor Cell**
- Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeting Tumor Angiogenesis

1. **Cancer cells release growth factors that activate endothelial cells during the transition to the angiogenic phenotype.** This occurs in response to acquired gene mutations and hypoxia.

2. **Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation.**

3. **Sprouting vessels secrete metalloproteinases (MMPs) and migrate towards the tumor using specific cell integrins.**

4. **Tumor blood vessels are characterized by turbulence, stasis, and leakage; blood flow is uneven and chaotic, with areas of tumor necrosis, hypoxia, and apoptosis.**

Metastases exit through the tumor vasculature to the systemic circulation.