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Review Article

Angiogenesis inhibitors in cancer therapeutics

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ABSTRACT

In the era molecular pharmacology, development of angiogenesis inhibitors is certainly a master discovery .There are specific angiogenesis inhibitors are being used in cancer and various endogenous anti-angiogenesis molecules are discovered .This review is a coverage of basic anti-angiogenic molecule like bevacizumab and other newer targets, after explaining the basic physiology of new vessel formation which helps in better understanding of these drugs.

Keywords: Angiogenesis, Angiogenesis inhibitors, Cancer

INTRODUCTION

Development of new blood vessels is a critical process in embryonic development, tissue repair, in the development of collateral circulations. Angiogenesis is also a major pathologic factor, in particular in cancer cell growth and metastasis and also in various other disease processes like neovascularization of retina etc. Checking the growth of excess angiogenesis is one the main target of drug development. Many angiogenesis inhibitors have been developed and some are in various stages of clinical trials.

ANGIOGENESIS

Most important factors that induce angiogenesis are VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor). VEGFs bind to a family of receptors (VEGFR-1, -2, and -3) with tyrosine kinase activity. The most important of these receptors for angiogenesis is VEGFR-2. VEGF stimulates proliferation of endothelial cells, thus initiating the process of capillary formation, PDGF and other factors such as transforming growth factors, angiopoientins 1 and 2, fibroblast growth factors helps in stabilization of newly formed blood vessels by allowing smooth muscle proliferation and connective tissue formation in blood vessels. Most important stimulating factor for VEGF production in hypoxia inducible factor 1 (HIF1).

ABERRANT ANGIOGENESIS IN TUMOURS

When tumor cells arise in, they grow to a size limited by hypoxemia and nutrient deprivation. Hypoxemia, a key regulator of tumor angiogenesis, causes the transcriptional induction of the gene encoding VEGF, which simultaneously stimulates HIF -1. Blood vessels developed in the tumors are tortuous, dilated and highly

leaky due to sparse basement membrane unlike normal vasculature, thus facilitates invasion and metastasis.[2]

ANTI ANGIOGENIC THERAPY

In experimental systems, anti-angiogenic molecules lead to changes in the tumor vasculature that has been termed vessel normalization. During the first week of treatment, abnormal vessels are eliminated, leaving a normal branching pattern and thick basement membrane coverage. These changes lead to a decrease in vascular permeability. Continuing anti-angiogenic therapy which is often combined with chemo- or radiotherapy, leading to tumor cell death.[2]

ANGIOGENIS INHIBITORS IN CANCER MANAGEMENT

Bevacizumab

Bevacizumab was the first angiogenesis inhibitor that was developed to arrest tumor growth. It is a humanized monoclonal antibody against vascular-endothelial growth factor (VEGF) and inhibits its interaction with the VEGFR1[3]. Bevacizumab is approved by the FDA for treatment of metastatic colorectal cancer in combination with 5-fluorouracil. There also is evidence of anti-tumor activity of bevacizumab in clear-cell renal cancer, non–small cell lung cancer and breast cancer in combination with chemotherapy.

Bevacizumab is administered IV every 2–3 weeks, its half-life is nearly 20 days.

Hypertension is the significant adverse effect noted during treatment, nearly ten percent of patients requires treatment for hypertension.[2,3] An increased risk of hemorrhage was noted in lung cancer patients with a squamous histology and large central tumors near the major mediastinal blood vessels. Other serious complications include bowel perforations that have been observed in 1–3% of patients mainly those with colon and ovarian cancers.

Sorafenib and Sunitinib

These two molecules are multiple tyrosine kinase inhibitors, with potent activity against VEGF and PDGF receptors. They Inhibit VEGF receptor associated signaling and limits angiogenesis. These molecules are targeted against renal cancer, liver cancer and gastro intestinal stromal tumor.[2,4]

NEWER MOLECULES OF ANTI ANGIOGENISIS

Vandetanib

It is a tyrosine kinase inhibitor of a number of cell receptors, mainly the vascular endothelial growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR).

It is well absorbed orally and having half-life of about 14-19 days. It is approved by FDA for medullary thyroid cancer, given 300 mg once or twice daily. Common side effects include abdominal pain and diarrhoea, rashes, prolonged QT interval, hypertension, headache.

Vandetanib is now under phase II study, where it is given with temozolomide and radiotherapy at the dose of 100 mg daily for glioblastoma.[5]

Axitinib

This tyrosine kinase inhibitor inhibits multiple targets, including VEGFR-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor.

In the trial with renal cancer enrolled patients, 361 patients were assigned to receive axitinib 5 mg orally twice daily, and 362 patients were assigned to receive sorafenib 400 mg orally twice daily. The final analysis demonstrated a statistically significant improvement in patients receiving axitinib compared with patients receiving sorafenib. On January 2012, FDA approved axitinib for the treatment of advanced renal cell carcinoma after the failure of one prior systemic therapy.[6]

The most common adverse reactions in patients treated with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome. Other severe adverse reactions reported in patients treated with axitinib included hypertensive crisis, thrombotic events, hemorrhage, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome.

Pazopanib

It is anti VEGF molecule have been approved for, soft tissue sarcoma.[7]

The approval is based on a randomized double-blind placebo-controlled multicenter trial in patients with metastatic soft tissue sarcoma who had received prior chemotherapy, including an anthracycline. The trial enrolled 369 patients who were randomly allocated (2:1) to receive pazopanib hydrochloride 800 mg orally once daily (N=246) or placebo (N=123). Forty-three percent of patients had leiomyosarcoma, 10 percent had synovial sarcoma, and 47 percent had other soft tissue sarcomas. A statistically significant improvement in progression-free survival (PFS) in patients receiving pazopanib hydrochloride compared with those receiving placebo was demonstrated. QT prolongation and hepatotoxicity are the significant adverse effects seen with this drug.

Aflibercept

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

It has been approved in Europe for use in the treatment of metastatic colorectal cancer.[8,9] Aflibercept is also in a phase III trial for hormone-refractory metastatic prostate cancer . Bleeding is the significant adverse effect.

Cilengitide

Cilengitide has been the first integrin-receptor antagonist to enter clinical development. Data from phase I studies have shown activity in recurrent glioblastoma.[10,11] This drug selectively binds the cell surface receptors $\alpha v\beta_3$ and $\alpha v\beta_5$, which are expressed on activated endothelial cells during angiogenesis and inhibits them.

Other anti angiogenic molecules and approaches

Beside these five agents, there are FEW molecules are investigated to inhibits angiogenesis. These include,[12,13]

- Thrombospondin (tsp-1)-for glioma
- XL-184 (BMS-907351)-for medullary thyroid cancer
- Tandutinib-for acute myeloid leukemia

CONCLUSION

Angiogenesis inhibitors are of no doubt, so valuable molecules in the treatment of various metastatic cancers. Additions of these molecules in the standard chemo or radiotherapy have been found to increase prognosis of cancer patients. The ideal molecule without serious concerns of adverse effects of anti VEGF molecules like hypertension, bleeding is yet too discovered. Currently endogenous anti-angiogenic molecules like arrestin, endostatin, canastatin are being targeted for drug development.

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