Research Article

Anti- Angiogenesis: A New Therapeutic Strategy in Oncology

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ABSTRACT

Angiogenesis is the formation of new capillary blood vessels from existing vasculature. Healthy individuals can harbour microscopic tumours and dysplastic foci in different organs in an undetectable and asymptomatic state for many years. These lesions are dependent upon angiogenesis for their growth. Inhibition of angiogenesis can slow, halt, or regress tumours. Targeting process of angiogenesis before clinical manifestation can prevent tumour growth and progression. Anti-angiogenesis therapy is based on the shutdown of this ability of tumour cells to form new blood vessels, thereby cutting its source of food. The therapy has proven to be more effective compared to radiational therapy, as radiational therapy results in the damage of subsidiary cells which in turn lead to the prevalence of necrosis. Finally, angioprevention may go well beyond cancer in the prevention of a range of chronic disorders where angiogenesis is crucial, including different forms of inflammatory or autoimmune diseases, ocular disorders, and neurodegeneration.

Keywords: Angiogenesis, tumour, necrosis, radiational therapy, autoimmune diseases.

INTRODUCTION

Today we are better able to treat cancer than ever. More than half of all people with cancer now live at least 5 years after being diagnosed. But cancer treatment is still far from perfect. The treatments we use, like chemotherapy, can sometimes cause severe side effects that can affect a person's quality of life. Patients and doctors have long hoped for cancer treatments that would work as well or better than the ones we use now but with fewer side effects. Scientists have learned a great deal in recent years about what makes cancer cells different from normal cells in the body. This has helped them find targeted drugs – drugs that focus on the cancer cells without having major effects on normal cells in the body. One promising cancer treatment to come from this research is called anti-angiogenesis treatment[1].

Angiogenesis is the formation of new blood vessels. (The term comes from 2 Greek words: angio, meaning blood vessel, and genesis, meaning beginning). This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels[2] and it naturally occurs in reproduction, the healing process of wounds and in the development of the embryo. Angiogenesis regularly occurs during growth and development in children but happens less often in adults. Otherwise, angiogenesis in adults is usually part of a disease process such as cancer[3].Cancer cells have the ability to invade and colonize new areas in the body. In order to grow beyond a few millimetres in size and metastasize, a tumour cell requires blood supply. They achieve this by stimulating angiogenesis where the tumour recruits new blood vessels by giving off chemical signals which supply nutrition to the tumour[2]. As the angiogenesis is necessary in the growth and spread of cancer, each part of the angiogenesis process is a potential target for new cancer therapies. The assumption is that if a drug can stop the tumour from receiving the supply of nutrients, the tumour will "starve" and die. Drugs that stop angiogenesis have become an important part of cancer treatment for many types of cancer[3].

The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed[2].

Drugs that are designed to stop angiogenesis are called angiogenesis inhibitors or anti-angiogenesis drugs[3]. Tumour blood vessels are distinct from normal resting blood vessels, and the distinctness of these special tumour vessels features them as good targets for cancer therapies[4]. By doing this, they may help prevent new tumours from growing. They

may also make large tumours shrink if their blood supply is cut off[5].

Mechanism of action

Scientists have found a number of different pathways that cancer cells can use to cause blood vessel growth. Each step in these pathways is a possible target for cancer treatment. Different drugs may work at different steps in these pathways like inhibiting synthesis of angiogenic proteins by cancer cells, neutralizing the angiogenic proteins, inhibiting the receptors of endothelia for angiogenic proteins, or directly inducing endothelial cell apoptosis. The therapeutic antibodies and small molecules both capable of targeting angiogenic growth factors, such as VEGF and bFGF, or angiogenic growth factor receptors, such as VEGFR and PDGFR, ECM proteins, ECM receptors, and their signal transduction pathways involved in the regulation of angiogenesis can be potential targets for angiogenesis therapy[6,7]. For example, one of the most important proteins in new blood vessel growth is vascular endothelial growth factor (VEGF). This protein is not made in large amounts by normal cells, but some cancer cells make it and release it into the area around them[8]. Since VEGF plays an essential role in stimulating tumour angiogenesis, blocking VEGF-mediated signalling pathways has been one of the major strategies for ant angiogenesis therapy. Currently, there are six members in the VEGF family (i.e., VEGF-A, -B, -C, -D, -E) and PlGF. These VEGF proteins bind in a distinct pattern to three structurally related receptor tyrosine kinases known as VEGF receptor (VEGFR)-1, -2, and -3. Monoclonal antibodies against VEGF or VEGFR and small molecule inhibitors of VEGFR tyrosine kinase (and its downstream signal transduction pathway) are some of the major antiangiogenesis therapeutic agents.[6, 7]

Classification of drugs

Although hundreds of antiangiogenesis therapeutic agents are under investigation, the FDA currently has approved only 14 anticancer drugs with recognized antiangiogenic properties. Based on therapeutic targets, these agents can be grouped into four major categories: monoclonal antibody therapies, small-molecule RTK inhibitors, mTOR inhibitors, and Other angiogenic agents.

- **Monoclonal Antibodies**
  These agents work by binding biologically active forms of angiogenic stimulators or their receptors and inhibiting endothelial cell proliferation and angiogenesis. Adverse effects of monoclonal antibody therapy are usually fairly mild. Side effects can include fever, chills, weakness, headache, nausea, vomiting, diarrhoea, low blood pressure, and rashes (TABLE 1)[9].

Table 1: Monoclonal Antibodies

Drug(Brand)	FDA approved indications	Dosing in normal adults	Precautions
Bevacizumab (Avastin)	Glioblastoma	10mg/kg i.v every 2 wk	Black box warnings: GI perforations, surgery and wound healing impairment, serious or fatal haemorrhage Additional precautions: serious or fatal non-GI fistula formation, arterial thromboembolic events(stroke,MI, TIA) , severe hypertension, proteinuria, nephritic syndrome, left ventricular dysfunction, infusion reactions
	Metastatic breast cancer	10mg/kg i.v every 14 days in combination with paclitaxel	
	Metastatic colorectal cancer	5-10mg/kg i.v every 14 days in combination with IV 5-FU based chemotherapy	
	Metastatic renal cell carcinoma	10mg/kg i.v every 14 days in combination with interferon alpha	
	Nonsquamous NSCLC	15mg/kg i.v every 3 wk in combination with carboplatin and paclitaxel	
Cetuximab (Erbitux)	Colorectal cancer	As monotherapy or in combination with irinotecan initial: 400mg/m^2 IV over 120 min Maintenance: 250mg/m^2 IV over 60 min	Black box warnings: life threatening infusion reactions, cardiopulmonary arrest Additional precautions: interstitial lung disease, dermatologic toxicity and infection, hypomagnesemia, hypocalcemia, hypokalemia, photosensitivity
	SCCHN	Monotherapy : 400mg/m^2 IV over 120 min Maintenance: 250mg/m^2 IV over 60 min once weekly	
Panitumumab (Vectibix)	Colorectal carcinoma	6mg/kg IV over 60 min every 14 days(doses higher than 1000mg should be administered over 90 min	Black box warnings: Dermatological toxicity and infection, infusion reaction. Additional precautions: Pulmonary fibrosis, hypomagnesemia, hypokalemia, photosensitivity.
Trastuzumab (Herceptin)	Adjuvant treatment of breast cancer	Following completion of Anthracyclines Initial:8mg/kg IV over 90min every wk	Black box warnings: Left ventricular dysfunction, infusion reaction, pulmonary toxicity. Additional precautions: Severe neutrophilia in combination with myelosuppressive agents.
	Metastatic breast cancer	Initial 4mg/kg IV over 90min given alone or in combination with paclitaxel. Maintenance:2mg/kg IV over 30min,	

		given once weekly until disease progression.	

5-FU: 5- flurouracil, GI: gastro intestinal, EGFR: Epidermal growth factor receptor, MI: myocardial infarction, min-minute, NSCLC: non-small cell lung cancer,SCCHN: squamous cell carcinoma of the head and neck, TIA: transient ischaemic attack.

- **Small-Molecule RTK Inhibitors**
  This is currently the largest class of drugs that block angiogenesis. These agents have the advantages of hitting multiple targets, oral administration, and potential for lower cost. Lack of target specificity leads to unexpected toxicity but also promising efficacy. Toxicity, notably fatigue, leads to discontinuation in 38% of patients treated with sunitinib. Hypertension, haemorrhage, and cavitations are common toxicities among this class of agents. Rash, fatigue, myalgia, and hand-foot syndrome are more specifically seen with RTK inhibitors. A major adverse effect with the EGF RTK inhibitors is an acne like rash (TABLE 2).[10, 11]

Table 2: Small Molecule RTK Inhibtors

Drug (Brand)	FDA approved indications	Dosing in normal adults	Precautions
Erlotinib (Tarceva)	NSCLC	150MG po daily without food	Pulmonary toxicity, dehydration and acute renal failure, hepatic failure, GI perforations, dermatologic effects, cardiovascular effects
	Pancreatic cancer	100mg po daily without food(used in combination with gemcitabine)	
Sorafenib(Nexavar)	Advanced renal cell carcinoma, hepatocellular carcinoma	400mg po twice daily without food.	Cardiac ischaemia,severe bleeding,hypertension, dermatologic toxicities,GI perforations.
Sunitinib (Sutent)	Advanced renal cell carcinoma.GIST	50mg po once daily on a schedule of 4 wk on treatment followed by 2 wk off. Adjusting in 12.5mg increments is recommended based on individual safety and tolerability	Left ventricular dysfunction, QT prolongation, severe hypertension, bleeding, hypothyroidism, hepatic failure, thrombotic microangiopathy.
Gefitinib (Iressa)	NSCLC	250mg po daily	Interstitial lung disease, common ADEs like diarrhoea, rash, acne, dry skin
Lapatinib (Tykerb)	HER 2-positive metastatic breast cancer	1,250 mg po daily on days 1-21 in combination with capecitabine 2,000 mg/m^2/day(administered orally in 2 divided doses 12h apart) on days 1-14 in a repeating 21 day cycle	Black box warning: Hepatotoxicity Additional precautions: left ventricular dysfunction, QT prolongation, severe diarrhoea, interstitial lung disease
	Hormone receptor-positive, HER2- positive metastatic breast cancer	1,500mg po daily continuously in combination with letrozole 2.5 mg po daily	
Pazopanib (votrient)	Renal cell carcinoma	800mg po daily without food	Black box warning: severe hepatotoxicity Additional precaution: avoid the concomitant use of strong CYP3A4 inducers or inhibitors; QT prolongation, haemorrhage, stroke, MI, hypertension

- ADEs: Adverse drug effects, GI: Gastro intestinal, GIST: GI Stromal tumour, HER2: Human epidermal growth factor receptor2, MI: Myocardial infarction, NSCLC: Non-small cell lung cancer, RTK: Receptor tyrosine kinase

- **mTOR Inhibitors**
  These agents represent a third, smaller category of antiangiogenic therapies with two FDA-approved agents, temsirolimus (Torisel) and everolimus (Afinitor). PI3K/Akt/mTOR is one of the three major signalling pathways that have been identified as important in cancer. mTOR is a key kinase downstream of PI3K/Akt, which regulates tumour cell proliferation, growth, survival, and angiogenesis. Since the PI3K/Akt/mTOR pathway is also essential for metabolism, insulin, and insulin growth factor (IGF) signal transduction, hyperglycemia, hypercholesterolemia, and hyperlipidemia are major adverse effects for this drug class. Other common adverse events for temsirolimus and everolimus include fatigue, stomatitis, diarrhoea, hypophosphatemia, low red blood cells and platelets, and peripheral edema. These adverse events are commonly reversible upon treatment discontinuation. Less common symptoms are renal insufficiency, interstitial pneumonitis, and low white blood cells (TABLE 3).[9, 12]

Table 3: mTOR inhibitors

Drug(Brand)	FDA approved indications	Dosing in normal adults	Precautions
Temsirolimus (Torisel)	Advanced renal cell carcinoma	25mg infused IV over a 30-60-min period once weekly. Dose reduction required for hematologic or NCI grade 3-4 toxicities. Premedicate with a prophylactic IV antihistamine for 30 min before the start of each dose	Hyperglycemia, immunosuppression, interstitial lung disease, hyperlipidemia, GI perforation, renal failure, intra cerebral haemorrhage, neutropenia, avoid exposure to live vaccine
Everolimus (Afinitor)	Advanced renal cell carcinoma	10 mg po daily at the same time every day	Black box warnings: immunosuppression, nephrotoxicity, renal graft thrombosis Additional precautions: avoid the concomitant use of strong CYP3A4 inducers or inhibitors; avoid exposure to live vaccine, non infectious pneumonitis, oral ulceration, decreased haemoglobin, hyperlipidemia, hypertriglyceridemia
GI: Gastro intestinal mTOR: mammalian target of rapamycin NCI: National cancer institute			

- **Other angiogenic agents**
  Bortezomib (Velcade) and thalidomide (Thalomid) may indirectly inhibit angiogenesis through mechanisms that are not completely understood (TABLE 4).[9, 13]

Table 4: Other angiogenic agents

Drug(Brand)	FDA approved indications	Dosing in normal adults	Precautions
Bortezomib (Velcade)	Mantle cell lymphoma[a]	1.3 mg/m^2 as a 3-5 sec IV injection twice weekly for 2 wk followed by a 10 day rest period	Peripheral neuropathy, hypotension, left ventricular dysfunction, pulmonary toxicity, constipation, diarrhoea, ileus, thrombocytopenia, herpes reactivation
	Multiple myeloma[a]	Previously untreated: 1.3 mg/m^2 as a 3-5 sec IV injection of a 32 day treatment cycle for 4 cycles, followed by a 42 day treatment cycle for 5 cycles in a combination with oral melphalan and oral prednisone	
Thalidomide (Thalomid)	Multiple myeloma	200mg po daily with water preferably at bed time and atleast 1 hr after the evening meal. Give in combination with dexamethazone 40mg po daily. Dose adjustment may be required for constipation, oversedation, or peripheral neuropathy	Black box warning: severe life threatening human birth defects, venous thromboembolic events, drowsiness, somnolence, orthostatic hypotension, stevens-johnson syndrome, seizures
a- Dose adjustment for neuropathies and grade 3 nonhaematologic or grade 4 haematologic toxicities.			

In some ways, anti-angiogenesis treatment is like chemotherapy. Both are forms of systemic treatment. This means that both treatments use drugs that travel throughout the body to have their effects. But anti-angiogenesis drugs do not work the same way chemotherapy does. Because of this, they differ in terms of what side effects they may cause and how well they work[14].

Side effects

Initially, it was thought that angiogenesis inhibitors would have mild side effects, but more recent studies have revealed the potential for complications that reflect the importance of angiogenesis in many normal body processes, such as wound healing, heart and kidney function, fetal development, and reproduction[2.] For example, many angiogenesis inhibitors raise a person's blood pressure. Although this side effect can be serious, it is treatable with medication. Rarely, these medications may cause serious bleeding, heart attacks, heart failure, or blood clots. People at higher risk for these conditions should discuss the risks and benefits of these treatments and ways to monitor these risks. (For example, patients who have had chemotherapy with a class of drugs called anthracyclines or radiation therapy to the chest wall, have a higher risk of congestive heart failure with bevacizumab.)[3]

Other side effects of these drugs may include a rash and/or dry, itchy skin, hand-foot syndrome (tender, thickened areas on the skin, sometimes with blisters on palms and soles), diarrhoea, fatigue, and low blood counts. Angiogenesis inhibitors can also

interfere with wound healing and cause cuts to re-open or bleed. Rarely, perforations (holes) in the intestines can occur. These are called bowel perforations and usually require surgery to correct. Although some side effects may be common, they do not happen with every drug or with every person. And it is found that, when they are given at low doses over a longer period of time they seem to work without causing major side effects (as opposed to giving high doses at regular intervals, which is how they are usually used)[3].

CONCLUSION

By observing the above description, Cancer survival tends to be poorer in developing countries, most likely because of a combination of late diagnosis and limited access to standard treatment. Chemotherapy drugs can be useful in treating many types of cancer, but some cancers do not respond well to them. In some cases, anti-angiogenesis drugs may prove to be a better option. For example, chemotherapy isn't helpful against kidney cancer. But doctors have long known that kidney tumours tend to form many blood vessels. Anti-angiogenesis drugs, such as sunitinib (Sutent) and sorafenib (Nexavar), have been shown to be useful against this type of cancer. Many doctors now consider these drugs to be the best treatments when systemic therapy is needed. Because of the way anti-angiogenesis drugs work, they are only useful in treating cancers that form tumours. They won't work against blood cancers like leukemias[15]. In addition to the angiogenesis inhibitors that have already been approved by the FDA, others that target VEGF or other angiogenesis pathways are currently being tested in clinical trials. If these angiogenesis inhibitors prove to be both safe and effective in treating human cancer, they may be approved by the FDA and made available for widespread use. In addition, phase I and II clinical trials are testing the possibility of combining angiogenesis inhibitor therapy with other treatments that target blood vessels, such as tumour-vascular disrupting agents, which damage existing tumour blood vessels[16].Yet, rigorous studies has to be made to find out the most opt combination for the treatment of Cancer.

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