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## Angiogenesis and Cancer: Recent Advances

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Recent studies have shown the possibility to treat cancer with drugs that affect the formation of new blood vessels instead of attacking directly the malignant cell. This relatively new field in the area of oncology on angiogenesis inhibition has expanded the therapeutic option for malignant diseases. We will discuss several anti-angiogenesis drugs in clinical development and their mechanism of action. Some of these drugs include:

angiostatin, metalloproteinase inhibitors, thalidomide, tamoxifen, interferons and others. The use of anti-angiogenic agents, both in combination with other treatment modalities in the acute setting as well as long-term maintenance or prevention of cancer, is at present one of the better promises in the war against cancer.

*Key word: Angiogenesis, Angiostatin, Endostatin, Neovascularization*

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**T**he potential to treat cancer with drugs that affect the formation of new vessels by the tumor has expanded in the past years. It is known that tumors cannot exceed 1-2 mm in size without a new blood supply; and the blood vessels not only provide oxygen and nutrients to the tumor but also serve as a route for metastases (1). For the past 30 years, Dr. Judah Folkman and his colleagues in the Boston Children's Hospital have investigated the field of angiogenesis but not until recently it has become evident that inhibiting this complex process holds a promise as a new tool to fight cancer (2,3).

Angiogenesis refers to the process in which new blood vessels form from preexisting vessels. It also plays a role in normal physiologic actions such as embryonic development and wound repair and also in non-malignant diseases such as diabetic retinopathy and rheumatoid arthritis. Malignant cells are genetically complex and develop quite rapidly drug resistance for which controlling the endothelial cells within a tumor is an important way to prevent further tumor growth and dissemination. By experimental models developed by Dr. Folkman, it is known that a single blood vessel can nourish 100 malignant cells (4,5). Therapies that impair the process of angiogenesis can arrest tumor growth, as was shown by Dr. Folkman in mice models. These discoveries caused an enthusiastic reaction and major USA newspapers such as the New

York Times published that the cure for cancer was going to be in the next two years with the use of a substance called angiotastin (6). However, Dr. Folkman clarified that his laboratory was curing cancer only in mice and that curing a disease in laboratory animals is not the same as doing it in humans.

Angiogenesis in the adult is in a steady state and for new blood vessel formation within a tumor this process has to be "switched on" by specific molecules initially known as tumor angiogenesis factors. Some of the known endogenous regulators of angiogenesis include: bFGF (basic fibroblast growth factor), VEGF (vascular endothelial growth factor), transforming growth factors alpha and beta, angiopoietin, androgens, estrogens, interleukins and metalloproteinases. Those factors are controlled by endogenous anti-angiogenic factors such as thrombospondin-1, angiostatin, endostatin, vasostatin, interferons and others. Mutant proteins produced by the tumoral cells (such as ras proteins) can upregulate the expression of pro-angiogenic factors and affect endogenous angiogenesis inhibitors (7). Not only the tumor cells release molecules that stimulate endothelial cell proliferation, but also endothelial cells release substances that promote tumor growth and invasion. We will discuss several anti-angiogenesis drugs in clinical development and their mechanism of action (8,9) (Table 1).

**Angiostatin.** Angiostatin was isolated by Dr. Folkman from the urine of mice injected with cancer cells. It is a proteolytic degradation product of plasminogen, but does not have anticoagulant properties. This protein inhibited metastases by preventing blood vessel formation (10).

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**Table 1.** Angiogenesis Inhibitors

Endogenous angiogenesis inhibitors	Angiostatin, endostatin, vasostatin, interferons
Exogenous angiogenesis inhibitors	Thalidomide, squalamine, paclitaxel, TNP-470
Matrix metalloproteinase inhibitors	Marimastat, tetracyclines, AG-3340
Anti-integrins	avB3 antibody
Direct growth factor inhibitors	Anti-VEGF
Signal transduction inhibitors	Calcium influx inhibitor, SU-5416

Later another substance with similar activities was isolated and named endostatin. Endostatin is a degradation product of collagen. Both endostatin and angiostatin have recently been used in human trials, and they are manufactured by EntreMed and the Boston Children's Hospital.

**Metalloproteinase inhibitors.** Metalloproteinases are enzymes that degrade the extracellular matrix in order to permit the passage of tumor cells through the tissue. Naturally occurring inhibitors of metalloproteinases are found in many tissues and inhibit angiogenesis, tumor growth and metastases. Several substances, such as Marimastat, Neovastat (squalamine), BB-94, tetracyclines, etc, are being tested as metalloproteinase inhibitors. Marimastat is being tested in breast cancer patients and is in development by British Biotechnology and the National Cancer Institute. Neovastat is derived from the cartilage of dogfish sharks and it has been tested in lung, breast and prostate cancer (11) and manufactured by Aeterna Laboratories.

**Thalidomide.** Thalidomide was initially introduced as a sedative and anti-emetic but was taken off the market when it was shown to induce fetal abnormalities by inhibiting blood vessel growth in the fetal limb bud. It has been studied in prostate cancer, breast cancer, Kaposi's sarcoma, glioma, melanoma, renal cancer, ovarian cancer, leukemias, myelodysplasias and multiple myeloma (12). It is also being investigated as a treatment for retinal neovascularization. An Eastern Cooperative Oncology Group protocol sponsored by the University of Wisconsin is presently investigating the combination of thalidomide with chemotherapy (paclitaxel and carboplatin) in locally advanced non-small cell lung cancer (13). As a prototype anti-angiogenic drug, thalidomide is not cytotoxic and can be given as a long-term therapy. The endpoint of studies using anti-angiogenic drugs should be survival and even if the primary tumor does not respond, they can control the development of metastases.

**Tamoxifen.** Tamoxifen is a selective estrogen receptor modulator which has been used for the treatment of breast cancer for the past decades. It has shown also anti-angiogenic properties, inhibiting the growth of tumor blood vessels. Tamoxifen was shown recently by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to

prevent the development of breast cancer in women at high risk (49% reduction in invasive breast cancer as compared to controls) (14). At present the San Juan CCOP (Community Clinical Oncology Program) through a National Cancer Institute grant is comparing tamoxifen with raloxifene as prevention

of breast cancer in high risk postmenopausal women. This trial, called the STAR (Study of Tamoxifen and Raloxifene for the Prevention of Breast Cancer) or P-2 trial, will randomize 21000 postmenopausal women in 400 centers in Canada, the United States and Puerto Rico. The anti-angiogenic properties of selective modulators of the estrogen receptor promise to have a substantial impact in the reduction of breast cancer incidence and in improving the general health of women.

**Interferons.** The anti-angiogenic potential of interferon alpha is known since 1988 when it showed to be effective for the treatment of hemangiomas in childhood (15). As with other anti-angiogenic agents, the treatment with interferon had to be long term and uninterrupted without the development of drug resistance. Interferon not only has an effect upon the blood vessels, but also have an effect directly upon the tumor.

**Chemotherapeutic drugs.** Many chemotherapeutic drugs, such as paclitaxel, irinotecan, topotecan also have an effect upon angiogenesis. This explains how metastases could be controlled in advanced cancer patients with long term treatment with chemotherapy without objective response in the primary tumor. This also can permit using chemotherapy at low doses with the goal of inhibiting angiogenesis without being directly toxic to the tumors.

**Other agents.** Other anti-angiogenic agents in pre-clinical and clinical trials include anti-integrins, direct growth factor inhibitors (anti-VEGF), exogenous angiogenesis inhibitors (TNP-470, AE941) and signal transduction inhibitors (calcium influx inhibitor, SU-5416 (8). Combretastatin, which is originally derived from the African bush willow, directly destroys tumor blood vessel cells (6).

## Conclusions

The use of anti-angiogenic agents, both in combination with other treatment modalities in the acute setting as well as long-term maintenance or prevention of cancer, promises to revolutionize oncology and is a real hope for controlling malignancies that until now have been refractory to present treatments. However, it is not known if prevention of neovascularization might affect long term wound healing, physiologic blood vessel growth or other normal

processes. Also, blocking a single agent may be inadequate since many factors are critical for tumor viability. Research trials must integrate other endpoints besides primary tumor response such as survival or improvement in quality of life. The exciting discovery that a tumor can be controlled by targeting the blood vessel versus the standard approach of destroying the malignant cell is at present the greatest promise in the war against cancer.

### Resumen

Estudios recientes han demostrado la posibilidad de tratar el cáncer con drogas que afectan la formación de nuevos vasos sanguíneos en vez de atacar directamente la célula maligna. Este campo de inhibición de angiogénesis, relativamente nuevo en el área de la Oncología, ha expandido las opciones terapéuticas para combatir las enfermedades malignas. Discutiremos varias drogas anti-angiogénesis en desarrollo clínico y su mecanismo de acción. Algunas de estas drogas incluyen: angiostatina, inhibidores de metaloproteínasa, talidomida, tamoxifén, interferones y otros. El uso de agentes anti-angiogénesis, tanto en terapia de combinación con otras modalidades de tratamiento en la etapa aguda como en el uso a largo plazo en mantenimiento o en la prevención del cáncer, es al presente una de las mayores promesas en la guerra contra el cáncer.

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