CONTINUING EDUCATION

Antiangiogenesis: The Fifth Cancer Treatment Modality?

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Purpose/Objectives: To describe the biologic process of angiogenesis and the potential role of antiangiogenesis therapy in cancer treatment.

Data Sources: Published articles, conference proceedings, and computerized databases.

Data Synthesis: Angiogenesis is the development of blood vessels. Antiangiogenic agents prevent the development of blood vessels, therefore preventing one mode of cancer metastasis. Clinical trials must be conducted to ascertain the most powerful antiangiogenic therapies. Trials combine chemotherapy, biotherapy, and radiotherapy with antiangiogenic therapy.

Conclusions: Information from animal studies has revealed that antiangiogenesis is a viable option in treating cancer and preventing metastasis. Although human studies are rare, preliminary results are promising, especially when antiangiogenesis is used in combination with current cancer treatment modalities.

Implications for Nursing: Nurses are in a unique position to teach patients about new treatments for cancer. Nurses must be knowledgeable about angiogenesis and the availability of potential antiangiogenesis agents. Nurses will be vital in collecting data in clinical trials, considering the subjective data that will be obtained.

Key Points . . .

- Angiogenesis is the development of blood vessels.
- Tumor growth and subsequent metastasis require persistent new blood vessel growth.
- Antiangiogenic agents prevent the development of blood vessels, therefore preventing one mode of cancer metastasis.
- Clinical trials with antiangiogenic agents may be difficult to conduct because typical end points involve time to progression or clinical improvement with subjective data such as decrease in pain or no further weight loss.

Goal for CE Enrollees:

To further enhance nurses' knowledge regarding angiogenesis.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the biologic process of angiogenesis.
2. Discuss the potential role of antiangiogenesis therapy in cancer treatment.
3. Discuss the implications for nursing practice with antiangiogenesis therapy.

Since the 1970s, research into the treatment of cancer has yielded numerous new modalities to combat cancer. Yet the biggest stumbling block to ensuring long-term survival is cancer metastasis. A patient with cancer is considered cured when cancer remains undetected for five or more years (van Eys, 1987). However, for some reason, over a period of time, cancer may begin to regenerate, and a patient can present with metastasis beyond that five-year period. The cause must be the result, in part, of cancer cells' ability to make their own blood supply or the stimulation of dormant micrometastasis through a process known as angiogenesis. Angiogenesis also has been implicated in the initial progression from a premalignant tumor to cancer. This article presents an overview of angiogenesis, including the regulation of angiogenesis, the process of tumor angiogenesis, and potential antiangiogenic therapy.

Definition of Angiogenesis

Angiogenesis is defined as the development of blood vessels. Angio means related to blood vessels, and genesis means development. Angiogenesis is fundamental to the reproduction, development, and repair of blood vessels. Blood vessels are formed from endothelial cells that connect to form a tubular structure to maintain blood flow and tissue perfusion. Normally, in an adult, blood vessels are formed from preexisting vessels such as capillaries through the process of angiogenesis (Volpert, 2000). This process is regulated tightly by numerous proangiogenic and antiangiogenic

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factors that act mainly on endothelial cells. As depicted in Figure 1, endothelial cells become stimulated from growth factors during angiogenesis. Once stimulated, some cells leave the capillary to divide and multiply. As a result, a new capillary sprout is formed from an existing capillary.

Accelerated angiogenesis is a normal physiologic response during wound healing, inflammation, and embryonic development. Apart from embryonic development and wound healing, angiogenesis is not crucial to continued healthy function in normal tissue (Hanahan & Folkman, 1996). Because the process by which normal angiogenesis occurs is the same for tumor angiogenesis, it is crucial to the growth of cancer cells (see Figure 2). The major difference between normal and pathologic angiogenesis is that normal angiogenesis ceases when the blood supply is met, whereas pathologic angiogen-

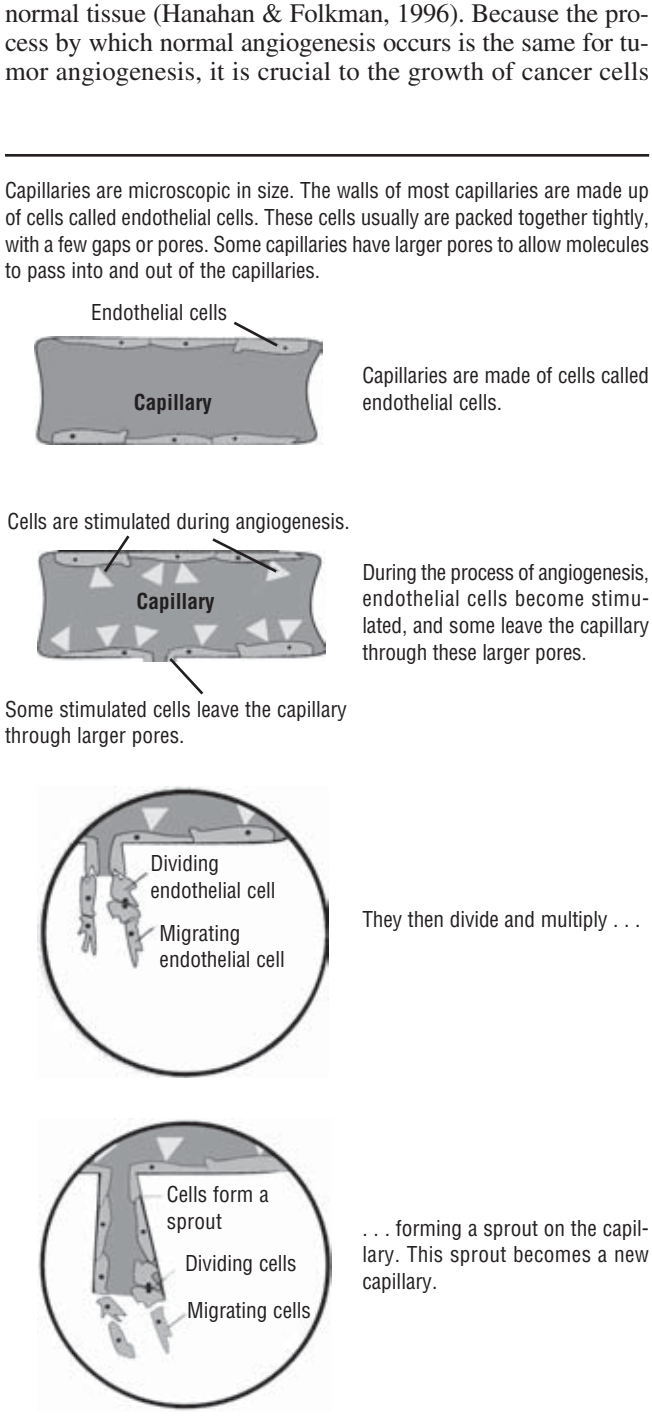

Figure 1. The Process of Angiogenesis

Note. From *Facts About Angiogenesis: A Natural Process That Can Contribute to Disease,* by Celgene Corporation, Warren, NJ. Copyright 1999 by Celgene Corporation. Reprinted with permission. All rights reserved.

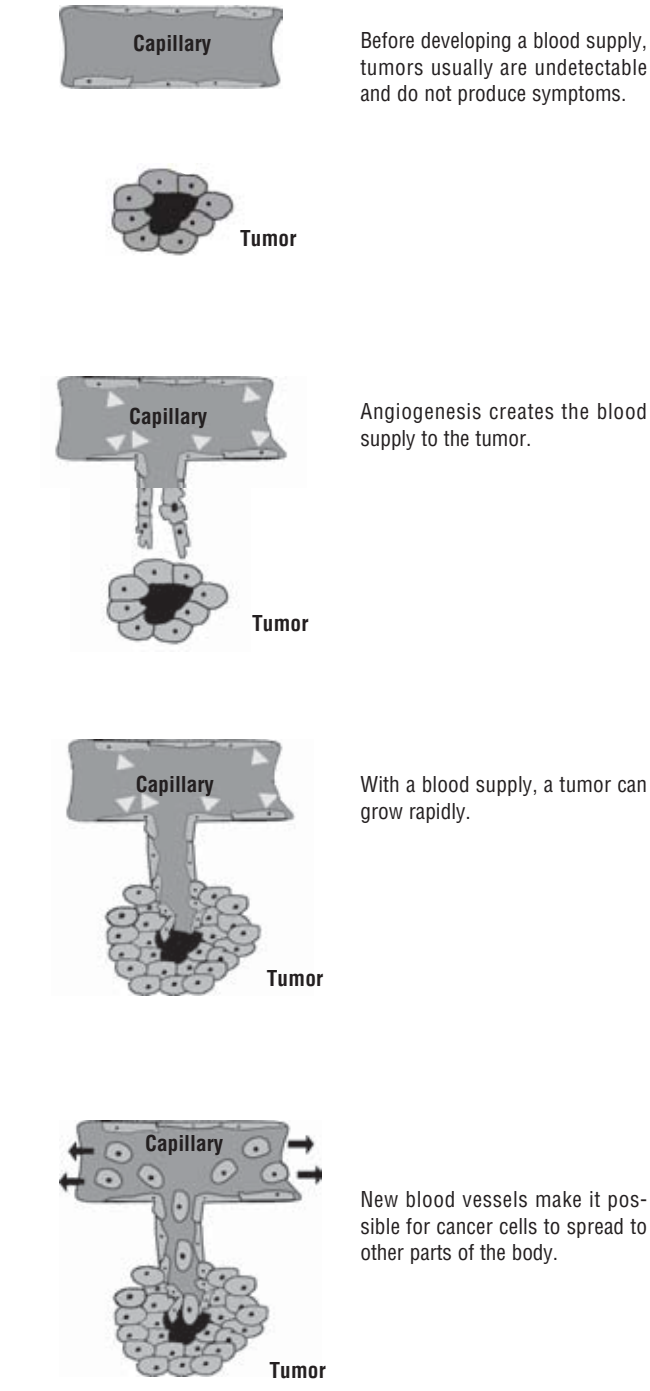

Figure 2. Angiogenesis and Tumor Growth

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esis continues to form blood vessels. The process of angiogenesis provides the pathway for tumors to create their blood supply. Pathologic accelerated angiogenesis occurs in diseases such as cancer, diabetic retinopathy, and rheumatoid arthritis (McNamara, Harmey, Walsh, Redmond, & Bouchier-Hayes, 1998). Stimulation from cancer cells can shift resting endothelial cells into a phase of rapid angiogenesis growth. When increasing amounts of antiangiogenic factors (inhibitors) are present, then proangiogenic factors (stimulators) are overruled, keeping the mechanism of angiogenesis turned off. If proangiogenic factors are more abundant than antiangiogenic factors, angiogenesis is stimulated (Semenza, 2000).

Regulation of Angiogenesis

Angiogenesis Promotion

Tumor growth and subsequent metastasis require persistent new blood vessel growth. This principle was confirmed by several experiments where cancer cells were implanted in vascular and avascular sites of animals (Brem, Brem, Folkman, Finkelstein, & Patz, 1976; Gimbrone, Leapman, Cotran, & Folkman, 1972; Hanahan & Folkman, 1996; Holmgren, O'Reilly, & Folkman, 1995; Parangi et al., 1996). Cancer cells implanted in vascular sites grew rapidly, forming large tumors by creating new capillaries. Cancer cells implanted in avascular sites were unable to form tumor masses and became necrotic, restraining the growth of tumors.

Tumor cells produce certain proangiogenic factors that have the ability to regulate metastasis either directly or indirectly (McNamara et al., 1998). Table 1 lists the better-known endogenous proangiogenic factors that control the process of angiogenesis (Hanahan & Folkman, 1996; McNamara et al.). These factors stimulate vascular endothelial cells by inducing new vascular networks from existing capillaries (Eckhardt, 1999). Proangiogenic factors are derived from tumor cells and infiltrating cells such as macrophages and growth factor-producing fibroblasts (Harmey, Dimitriadis, Kay, Redmond, & Bouchier-Hayes, 1998). In the development of a tumor, the angiogenic switch is associated with the onset of expression and secretion of proangiogenic factors by tumor cells.

The first proangiogenic factor to be discovered was the basic fibroblast growth factor (bFGF), followed by the acidic fibroblast growth factor (aFGF). Both proteins are members of a family of growth factors that is characterized by a high affinity for binding to heparin (Compagni, Wilgenbus, Impagnatiello, Cotten, & Christofori, 2000; Hanahan & Folkman, 1996). Recruited mast cells release heparin, which amplifies the effect on tumor growth and increased vascularity of bFGF and aFGF; aFGF and bFGF bind receptors on endothelial cells to stimulate proliferation, migration, and differentiation that induces angiogenesis (Compagni et al.).

Another secreted protein, discovered because of its ability to increase vascular permeability, is vascular endothelial growth factor (VEGF). Two related endothelial growth factors have been identified as VEGF-B and VEGF-C. All three of these growth factors are widely expressed in normal adult organs and as cell surface receptors on endothelial cells. VEGF and bFGF are commonly expressed by a wide variety of human cancers, including glioblastoma, chronic lymphocytic leukemia, acute promyelocytic leukemia, multiple myeloma, and colon, gastric, breast, lung, brain, hepatocellular, and bladder cancers (Folkman, 1995). Another proangiogenic growth factor, epidermal growth factor, is expressed by numerous solid tumors, including non-small cell lung, renal cell, breast, and head and neck cancers (Li et al., 1994; Poon, Fan, & Wong, 2001; Sheen-Chen, Chen, Sheen, Eng, & Chen,

Table 1. Proangiogenic Growth Factors

Growth Factor	Action(s)
Acidic fibroblast growth factor	Heparin-binding site causing a mitogenic effect on endothelial cells
Angiogenin	Unknown
Basic fibroblast growth factor	Stimulates endothelial cell growth
Cyclooxygenase-2	Increases expression of vascular endothelial growth factor (VEGF), stimulates endothelial cell migration
Endotoxin	Can elicit production of VEGF, basic fibroblast growth factor, transforming growth factor-beta, tumor necrosis factor, interleukin (IL)-1, and IL-6
Epidermal growth factor	Stimulates proliferation of many cell types, particularly epithelial and endothelial cells
Fibrin	Unknown
Fibronectin	Unknown
Hepatocyte growth factor (scatter factor)	Unknown
Hypoxia inducible factor-1	Expresses VEGF during hypoxia
IL 1, 4, 6, 8, 15	Unknown
Insulin-like growth factor	Stimulates cell metabolism, promotes cell survival
Matrix metalloproteinase	Degrades extracellular matrix
Platelet-activating factor	Unknown
Platelet-derived endothelial growth factor	Released during blood clotting cascade, stimulates proliferation of connective tissue cells and neuroglial cells
Prostaglandin E1 and E2	Unknown
TGF (alpha and beta)	Produced by macrophages and activated platelets, interferes with extracellular matrix formation
TNF	Broad spectrum of activity both as a stimulating and an inhibiting factor, induces granulocyte macrophage–colony-stimulating factor, procoagulant activity, increases the adherence of endothelial cells
Urokinase plasminogen activator	Unknown
Vascular integrin	Proteins that facilitate cell-to-cell interactions
VEGF	Most potent directly acting protein known that has specific mitogenic activity on endothelial cells

Note. Based on information from Compagni et al., 2000; Eckhardt, 1999; Folkman, 1995; Hanahan & Folkman, 1996; Harmey et al., 1998; Jung et al., 2000; McNamara et al., 1998; Poon et al., 2001; Semenza, 2000; Sheen-Chen et al., 2001.

2001). In hormone-sensitive tumors, estrogen, androgen, and progestin can increase the number of receptor sites for VEGF. When VEGF, bFGF, or epidermal growth factor is overexpressed, a subsequent increase in angiogenesis and resultant tumor growth occur.

Hypoxia is a primary stimulus for angiogenesis, leading to VEGF expression (Li, Shan, Cao, & Dewhirst, 2000). As solid tumors grow in size, the cells within the expanding masses frequently become hypoxic because of their increasing distance from the nearest blood vessels (Poon et al., 2001). Hypoxia develops when tumors grow beyond 2–3 mm in diameter. At this point, diffusion of oxygen from the host vasculature reaches its limit and hypoxic stress is significant enough to stimulate production of proangiogenic factors such as VEGF. Hypoxia-sensitive promoters, such as hypoxia inducible factor-1 and activating protein, regulate the production of VEGF (Li et al., 2000). As a result of VEGF production, new capillary pathways develop and deliver oxygen to the tumor bed (Semenza, 2000).

Angiogenesis Inhibitors

Endogenous inhibiting factors also exist and can influence one or several steps of angiogenesis. Table 2 lists the better-known endogenous antiangiogenic factors that inhibit the process of angiogenesis (Hanahan & Folkman, 1996; McNamara et al., 1998). Initially, exploration of endogenous angiogenesis inhibitors came with the observations that alpha interferon and platelet factor-4 could inhibit endothelial cell proliferation (Hanahan & Folkman). Through a series of experiments, researchers found that endogenous angiogenesis inhibitors can serve to counteract proangiogenic factors that grow new capillaries (Brouty-Boye & Zetter, 1980; Good et al., 1990; Rastinejad, Polverini, & Bouck, 1989; Taylor & Folkman, 1982). These experiments also found that inhibitors of angiogenesis could be controlled by tumor suppressor genes. Inhibitors may stop angiogenesis by (a) interfering with growth factor stimulation, (b) inhibiting endothelial cell proliferation, (c) inhibiting endothelial cell migration, or (d) inhibiting microtubule formation to sprout new capillaries (Cao, 2001).

The first inhibitor of angiogenesis, discovered in the late 1980s, was thrombospondin-1 (Good et al., 1990; Volpert, 2000). This inhibitor is secreted by a multitude of cells, including platelets, chondrocytes, osteocytes, and epithelial, endothelial, and stromal cells (Carpizo & Iruela-Arispe, 2000). Thrombospondin-1 acts by a variety of mechanisms, including blocking neovascularization and interfering with endothelial cell migration.

Another potent inhibitor of angiogenesis, called angiostatin, is recognized as a plasminogen fragment. Circulating angiostatin is able to sustain dormant metastases and primary tumors by blocking blood vessel growth through restriction of induced angiogenesis (O'Reilly et al., 1994). Angiostatin is believed to be a specific endogenous inhibitor with activity against VEGF, aFGF and bFGF that prevents endothelial cell migration (O'Reilly et al., 1994; Soff, 2000).

Process of Tumor Angiogenesis

Although not completely understood, angiogenesis involvement in cancer metastasis has been recognized for years. Once tumor growth exceeds 2–3 mm, an alternative blood supply is needed to deliver oxygen and nutrients and remove waste products (Eckhardt, 1999; McNamara et al., 1998). Without adequate blood supply, cancer cells cannot multiply; hence, cancer cannot metastasize through the blood

Table 2. Antiangiogenic Factors

Factor	Action(s)
Angiostatin	Internal fragment of plasminogen that inhibits endothelial cell proliferation
Antithrombin	Acts on proliferating endothelial cells
Arresten	Inhibits angiogenesis
Canstaten	Inhibits angiogenesis
Endostatin	Protein fragment of collagen XVIII that blocks collagenase and impedes matrix remodeling, inhibits endothelial cell proliferation
Granulocyte macrophage–colony-stimulating factor	Modifies tumor environment
Interferon alpha and beta	Suppresses angiogenesis by unknown mechanisms
Interleukin 12, 18	Unknown
Maspin	Unknown
Metallospondin 1-2	Alters extracellular matrix
2-methoxyestradiol	Inhibits endothelial cell proliferation
Neuropilin-1	Inhibits vascular endothelial growth factor
Pigment epithelium-derived factor	Unknown
Platelet factor-4	Unknown
Prolactin	Interferes with endothelial cells
Restin	Inhibits angiogenesis
Thrombospondin-1 and -2	Glycoprotein secreted by many cells, including endothelial, epithelial, and fibroblasts that decrease tumor endothelial cells' adhesiveness, motility, and proteolytic activity
Tissue inhibitors of metalloproteinase 1-2-3	Inhibits proteolytic activity of metalloproteinase
Transforming growth factors B-1	Unknown
Troponin-1	Unknown
Tumstatin	Inhibits angiogenesis
Vasostatin	Unknown

Note. Based on information from Cao, 2001; Carpizo & Iruela-Arispe, 2000; Eckhardt, 1999; Jung et al., 2000; Pribluda et al., 2000; Soff, 2000; Volpert, 2000.

circulation. Angiogenesis is not one event but rather a series of events involving the vascular endothelial cells. Once stimulation of angiogenesis occurs by proangiogenic factors, the process progresses in stages: basement membrane degradation, endothelial cell activation, proliferation, migration, and capillary lumen formation (McNamara et al.).

Cancer cells promote angiogenesis by overexpressing one or more positive regulators of angiogenesis, mobilizing an angiogenic protein from the extracellular matrix, and recruiting host cells such as macrophages (Folkman, 1995). At the cellular level, the onset of neovascularization augments tumor growth through a perfusion effect and paracrine effect. Perfusion in crowded tissue allows for nutrients and oxygen to enter and waste to exit more efficiently than diffusion. The paracrine effect results from the production of growth factors by capillary endothelial cells or their release by macrophages to a tumor (Li et al., 2000).

At this cellular level, continued vessel growth requires proteases, growth factors, and adhesion molecules (Eckhardt, 1999). An essential component of this new vessel invasion is the degradation of the extracellular matrix (basement membrane) surrounding the endothelial cell. Degradation of the extracellular matrix and fibrinolysis are performed by the pericytes and enzymes called matrix metalloproteases (MMPs) expressed by endothelial cells and tumor cells. Once degradation occurs, local tissue invasion facilitates endothelial cells to invade the stroma and migrate (Eckhardt). A lumen is formed from a vascular sprout through the joining of intracellular vacuoles facilitated by cell-to-cell adhesive contact. Vascular cell migration is promoted by cell adhesive receptors with collagen and fibronectin proteins (McNamara et al., 1998).

Endogenous and exogenous factors from tumor cells stimulate the release of cytokines. In turn, cytokines activate the release of endothelial cells. These endothelial cells begin to proliferate and migrate toward cancer cells. Endothelial cells express increased levels of integrin on the extracellular matrix protein receptor. Integrins are transmembrane glycoprotein receptors that mediate cell-to-cell adhesion, extracellular membrane interaction, and cell migration. Adhesion molecules, like integrins, are involved in angiogenesis by binding to glycoproteins present in the extracellular matrix or cell surface (Nangia-Makker, Baccarini, & Raz, 2000).

The endothelial cells cease proliferating and tightly adhere to each other to form a new capillary lumen and produce a new basement membrane (Hanahan & Folkman, 1996). Stabilization of the newly formed capillaries and basement membrane often is incomplete in tumors. This results in irregular vessels with partial endothelial linings and basement membranes (Miller, Sweeney, & Sledge, 2001). The failure of stabilization may be a result of persistent overexpression of the Tie 2 receptor antagonist angiopoietin-2 in the tumor-associated capillaries (Brown & Giaccia, 1998). Subsequently, tumor capillaries are leaky and interstitial pressure is increased because of the lack of lymphatic vessels (McNamara et al., 1998). Although newly formed tumor capillaries are unstable, the process of angiogenesis continues until the angiogenesis switch is turned off (Cao, 2001; Semenza, 2000). This allows for expansion and multiplication of the cancer cells and an eventual increase in tumor mass size.

Most tumors in humans are present in situ for months to years without neovascularization but then become vascularized when proangiogenic factors within the tumors stimulate the process of angiogenesis (Volpert, 2000). A tumor cannot shed cells into the circulation until the tumor mass has developed new blood vessels. Since the 1970s, laboratory and indirect clinical evidence has supported the role of angiogenesis in the progression and metastasis of many solid tumors such as those of the bladder, brain, breast, cervix, colon, lung, prostate, and testes (Miller et al., 2001; Semenza, 2000).

Uses of Antiangiogenic Therapy

In 1971, Folkman proposed antiangiogenesis as another modality in treating cancer. Theoretically, antiangiogenic therapy could induce long-term suppression of tumor angiogenesis by containing micrometastasis in a state of dormancy because antiangiogenesis therapy is cytostatic rather than cytotoxic. Therefore, antiangiogenic therapy could prevent a tumor from developing its own blood supply and prevent metastasis. Thus, antiangiogenic therapy could be an important consideration as a fifth cancer treatment modality.

Clinical trials with antiangiogenic agents may be difficult to conduct because typical end points involve time to tumor progression or clinical improvement with subjective data such as decrease in pain or no further weight loss. The clinical applications of angiogenesis research include the diagnosis and prognosis of cancer and the inhibition of angiogenesis with various antiangiogenic agents.

Angiogenesis activity may be useful as a prognostic tool and possibly a predictor of recurrence. Although studies have not been conclusive, compelling evidence shows that circulating angiogenic factors are of prognostic significance (Fontanini et al., 1997; Fujisaki, Mitsuyama, Toyonaga, Matsuo, & Tanikawa, 1998; Kraft et al., 1999; Weidner, Semple, Welch, & Folkman, 1991; Yamamoto et al., 1997). Tumor expression of angiogenic factors can be studied at the protein level by techniques such as immunohistochemical staining and Western blot analysis (Miller et al., 2001; Poon et al., 2001). For example, a strong association between high tumor VEGF expression has been correlated with poor survival (Poon et al.). Serum levels of transforming growth factor (TGF)-B1 were measured in 60 patients with breast cancer prior to surgery using immunoassay (Sheen-Chen et al., 2001). Data on the primary tumor, patient's age, estrogen receptor status, lymph node status, and distant metastasis were reviewed and recorded. Patients with more advanced cancer were found to have higher levels of TGF-B1. Thus, increased levels of TGF-B1 may reflect advanced breast cancer.

Cancer tissue is highly vascularized. As tumor grade increases, the proliferation of neovascularization becomes more prominent (Eckhardt, 1999). For instance, in breast and prostate cancers, vessel density in invasive cancers has been demonstrated to be a significant prognostic indicator. Vessel density refers to the degree of vasculature volume within the tumor bed (Weidner et al., 1991). If vessel density is low, prognosis is good; however, prognosis becomes poor with increasing blood vessel density within the tumor bed because of the potential for metastasis (Hanahan & Folkman, 1996).

Hematologic malignancies also reveal increased angiogenesis with increased vascular density in the bone marrow of patients with acute myelogenous leukemia and multiple myeloma (Vacca et al., 1994). Once such patients are in complete remission, vessel density returns to normal (Miller et al., 2001; Perez-Atayde et al., 1997).

Another potential clinical application of circulating angiogenic factors is monitoring for recurrent disease after primary treatment of cancer. For example, a fall in serum VEGF level has been documented after the surgical removal of breast, colorectal, and ovarian cancers (Fujisaki et al., 1998; Kraft et al., 1999; Yamamoto et al., 1997). Patients with no recurrence were found to have low levels of VEGF. However, patients with recurrence had a persistent VEGF elevation (Poon et al., 2001). Another study revealed that patients with cervical cancer had elevated serum bFGF for four months prior to clinical detection of disease recurrence (Sliutz et al., 1995). Although the number of patients evaluated was small, the potential role of monitoring circulating angiogenic factors for early detection of tumor recurrence is important.

Antiangiogenic Agents

The field of antiangiogenesis therapy was revolutionized with the discovery of angiostatin in 1994 (Soff, 2000). Angiostatin was found to be a specific endogenous angiogenesis inhibitor with activity against endothelial cells, VEGF, and bFGF. The discovery and identification of angiostatin was a tremendous advancement, but the exact source of angiostatin is unknown (O'Reilly et al., 1994). Although laboratory studies continue to explore the natural source of angiostatin, it is being evaluated in clinical trials for usefulness in cancer treatment.

Currently, clinical trials are studying antiangiogenic agents that inhibit growth factors, promoting endothelial proliferation and the proteases required for endothelial cells to penetrate the basement membrane (see Table 3). Antiangiogenic agents that may alter the cytokine microenvironment controlling the angiogenesis process also are in clinical trials (McNamara et al., 1998). For example, octreotide might inhibit tumor growth by interfering with the synthesis of autocrine growth factors simulated by tumor cells (Cascinu, Del Ferro, & Catalano, 1995). Cyclooxygenase-2 (COX-2) is an enzyme that is expressed by certain cancers. COX-2 can be induced by a variety of growth factors such as interleukin-1, tumor necrosis factor, epidermal growth factor, and TGF-B. Treatment with selective COX-2 inhibitors has been shown to induce antiangiogenesis of a variety of cancers, including colon, stomach, and prostate cancers, by blocking those growth factors (Gately, 2000; Masferrer et al., 2000).

Preclinical studies have shown that many of these endogenous and exogenous angiogenesis inhibitors block neovascularization in tumors at doses that do not produce toxicity in animals or humans (Cao, 1999, 2001; Gimbrone, Cotran, Leapman, & Folkman, 1974; Holmgren et al., 1995; Kim et al., 1993; O'Reilly, Holmgren, Chen, & Folkman, 1996). Interferon alpha 2 has been successful in the treatment of pediatric hemangioma (Kaban et al., 1999). Kaban et al. reported a child with a rapidly growing hemangioma with an abnormally elevated level of bFGF measured in her urine. Interferon alpha 2 was used to block bFGF from the tumor.

Table 3. Potential Targets of Antiangiogenic Agents

Potential Target	Antiangiogenic Agent
Anti-integrin agents	EMD 121974 Vitaxin
Cytokines	Interferon alpha 2 Interleukin-12 Somatostatin analogs
Endothelial inhibitors	AGM-1470 Angiostatin CA4P CM-101 Combretastatin A-4 Cyclooxygenase-2 inhibitors Endostatin Metastatin TNP-470 Squalamine
Matrix metalloproteinase inhibitors	AG 3340 Bay 12-9566 BMS 275291 COL-3 Marimastat Neovastat
Multiple functions	Thalidomide
Vascular endothelial growth factor (VEGF) antagonists	Anti-VEGF antibody HuMV833 PTK 787/ZK22584 SU-5416 SU-66668 Tamoxifen
Other: unknown targets	Carboxyamido-triazde IM 862 Carboxymethyl dextran benzylamide Suramin

Note. Based on information from Bagheri-Yarmand et al., 2001; Cao, 2001; Gately, 2000; Kaban et al., 1999; Kudelka et al., 1998; Volpert, 2000.

A synthetic analog of fumagillin, TNP-470 (an angiogenesis inhibitor), has been successful in the treatment of metastatic cervical cancer (Kudelka, Verschraegen, & Loyer, 1998). Thus far, antiangiogenesis agents appear to be safe with a low toxicity profile (Cao, 2001). Antiangiogenesis therapy must be administered for several months or years because the agents are cytostatic compared to other cancer modalities that are cytotoxic (Folkman, 1995). Therefore, chemotherapy, biotherapy, or radiotherapy in combination with antiangiogenic agents probably will be more effective than single-modality treatments.

Developing antiangiogenic therapy has been challenging. Although endothelial cells are located throughout the body, the cells perform different functions depending on body site (Jung et al., 2000). Endothelial cells at all body sites provide a protective and smooth surface within the vascular system for transport of various substances. For instance, hepatic endothelial cells and Kupffer cells line the venous sinusoids to phagocytize bacteria and other foreign material in the blood (Guyton, 1982). In the lungs, endothelial cells optimize oxygen transport

from the alveoli to the pulmonary blood stream (Guyton). Enormous implications for antiangiogenic therapy are based on the recognition that endothelial cells in different organs are phenotypically distinct. Thus, different tumors likely will respond differently to specific antiangiogenic treatments (Jung et al.). Combination antiangiogenic therapy may be necessary to maintain long-term suppression of tumor angiogenesis if different body sites are involved.

Another factor to consider is the tumor microenvironment within which angiogenic factors are being released by cancer cells. For example, melanoma expresses high levels of bFGF (proangiogenic factor) and low levels of interferon B (antiangiogenic factor). Thus, antiangiogenic therapy would need to focus on endothelial cell disruption as well as interfere with bFGF secretion (Jung et al., 2000). Identifying the specific factors that mediate angiogenesis in different organs may help to determine appropriate antiangiogenic treatment (Jung et al.). Another example, in a breast cancer cell-line model, is tamoxifen in combination with antiangiogenic agent carboxymethyl dextran benzylamide (CMD B7), where tumor growth was inhibited through a synergic effect (Bagheri-Yarmand, Hamma-Kourbali, Bissieres, Morere, & Crepin, 2001). Both agents exhibited action using different pathways in the angiogenesis process. CMD B7 has been found to inhibit endothelial proliferation and migration, whereas tamoxifen inhibits VEGF (Bagheri-Yarmand et al.).

Thalidomide appears to be an antiangiogenic agent that affects angiogenesis in multiple pathways. This drug has been shown to inhibit bFGF, VEGF, and tumor necrosis factor, and it interferes with endothelial cell functions. Because of these antiangiogenic properties, thalidomide is being studied in numerous malignancies, including multiple myeloma, acute myelogenous leukemia, gliomas, renal cell carcinoma, breast and prostate cancers, and melanoma (Stirling, 2000). Thus far, studies using thalidomide in multiple myeloma are yielding promising results (Alexanian & Weber, 2000; Rajkumar et al., 2000; Singhal et al., 1999; Vacca et al., 1994). High plasma levels of bFGF and VEGF have been found in patients with multiple myeloma, and thalidomide has been found to inhibit these growth factors. In addition, thalidomide may have a direct effect on multiple myeloma or bone marrow stomal cells to inhibit their growth and survival (Hideshima et al., 2000).

Because every class of chemotherapeutic agents has been reported to have antiangiogenic activity, combination therapy with an antiangiogenic agent seems reasonable (Miller et al., 2001; Schirner, 2000). Unfortunately, no set criteria define the antiangiogenic activity of chemotherapy agents. The ability to isolate and maintain endothelial cells in culture has allowed detailed study of endothelial proliferation, migration, and cellular function. Assays have been developed to measure chemotherapy agents' action on endothelial cells (Miller et al.; Schirner). Some agents may have profound antiangiogenic effects at low doses, yet others exhibit antiangiogenic activity only at high doses (Miller et al.). For instance, taxanes inhibit endothelial cell proliferation at concentrations lower than doses needed to kill tumor cells (Belotti et al., 1996). Chemotherapy may affect the production of cancer cells' proangiogenic factors that stimulate angiogenesis. For example, methotrexate has been found to decrease serum VEGF and vinblastine to decrease MMP secretion (Paleolog et al., 1998; Vacca et al., 1999). Vinca alkaloids exert the most toxic effects on the endothelium, causing defects and instability of the cell wall (Schirner). Antiangiogenic therapy is an appealing strategy for chemotherapy-resistant disease. Other combined modalities are possible as well. For example, angiostatin has been found to potentiate the radiation effect on cancer in mice (Gorski et al., 1998).

Gene therapy with endogenous angiogenesis inhibitors is a promising approach to antiangiogenic therapy (Cao, 2001). In principle, angiogenesis gene therapy targets the growing population of angiogenic endothelial cells (Varda-Bloom et al., 2001). The improvement of gene therapy has made it possible for the introduced gene to last for months or years in the body. Subsequently, gene therapy with an angiogenic inhibitor agent may reduce the need for prolonged administration of the agent. Results of several animal studies with gene therapy and antiangiogenic agents (e.g., angiostatin, endostatin, interleukin-12) are promising (Cao, 2001; Varda-Bloom et al.). Studies attempting development of a system to direct gene expression to endothelial cells that will be expressed specifically in the angiogenic vessels of solid tumors and metastases are ongoing (Cao, 2001; Nesbit, 2000; Varda-Bloom et al.).

The principle that tumor growth requires angiogenesis raises further questions. When is angiogenesis activated during tumor development? How can healthcare providers control the stimulus to turn off the angiogenesis process? What turns the angiogenesis stimulus on? What happens to a tumor when a patient must stop antiangiogenic therapy? How long will antiangiogenic therapy control tumor spread? Research must be continued to ascertain the answers to these questions and others.

Nursing Implications

Nobody knows what type of nursing care will be required to manage patients on antiangiogenic treatment. Oncology nurses' knowledge regarding factors and steps in the development of metastasis is basic to understanding antiangiogenic treatment. Oncology nurses must seek information about the biology, availability, potential benefits, and adverse toxicities of antiangiogenic treatment because patients and their families ask nurses for information and guidance. Patient education is essential to ensure that patients have appropriate information about antiangiogenic therapy.

The U.S. Food and Drug Administration has not approved any antiangiogenic agents as treatment for cancer. Nurses in clinical trials of antiangiogenesis agents can provide the necessary education to ensure informed consent. Nurses constantly must assess patients' understanding of antiangiogenic treatment. Information must be provided on administration route, mechanism of action, potential side effects, and self-care measures that can be employed to minimize those effects. When and to whom patients should report side effects must be communicated. A crucial role for clinical trials nurses is assessing for toxicities by inquiring about symptoms and performing physical assessments. Future trials will be based on these toxicities. Although antiangiogenic treatment has had low toxicity, using these agents in combination with other modalities will require astute monitoring and careful patient teaching regarding self-care measures and when to contact the clinic.

With any new cancer treatment, major obstacles will have to be overcome. Antiangiogenic treatment will be administered over a long period of time, perhaps over a patient's lifetime or until unacceptable toxicity occurs. The cost involved still is uncertain, as is whether these agents will be reimbursed by insurance. Increased time from healthcare professionals may be required to obtain these agents for patients.

Conclusion

Tumor angiogenesis is the result of complex interactions among tumor cells, endothelial cells, and growth factors. Recognition that tumor growth requires angiogenesis and ongoing identification of the factors that mediate angiogenesis have broadened understanding of the angiogenesis process, opening new avenues for cancer treatment. Researchers have limited technology and rudimentary information to begin combining antiangiogenesis agents with chemotherapy, biotherapy, or radiotherapy. Not all growth factors and their functions are understood. The future holds promise for the incorporation of gene therapy and the ability to monitor cancer progression with radiologic technology. When an effective antiangiogenic therapy is developed, it will be one of the most significant advances in multimodal cancer treatment and perhaps considered a fifth modality.

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