Keys to Unlock Cancer: Targeted Therapy

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For decades, perhaps even centuries, researchers have searched for a cure for cancer. The effort has taken many approaches, from surgery to cytotoxic or cytostatic chemotherapy to radiation therapy to agents that alter the cellular microenvironment to preventive measures, such as nutrition, screening, and medications. The ultimate goal of each intervention has been to specifically affect the malignant cells, leaving normal cells intact. Unfortunately, this simple concept has been difficult to implement. The problem has been two-fold: first, identifying a unique property of malignant cells (target) and second, developing an agent that interacts solely with that property. Agents developed to interact with such targets are called targeted therapy. Epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF) are two such targets.

A targeted therapy approach to the treatment of disease is not exclusive to cancer and has been used successfully in other disease processes. The science of targeted therapy in cancer has taken years to evolve, beginning with the pioneering work by Folkman that elucidated the role of angiogenesis in cancer to the discovery of a molecular marker, such as the Philadelphia chromosome in chronic myelogenous leukemia, to signal transduction research, which showed the importance of the human EGFR family in the growth and proliferation of malignancies. The journey has been long and arduous and is far from complete.

This article focuses on the function of the human EGFR family and VEGF-mediated angiogenesis and their role in therapeutic options for control of tumor growth.

Epidermal Growth Factor Receptors

The human EGFR family consists of four transmembrane receptors: EGFR (HER1/*erb* B-1), HER2 (*erb* B-2/*neu*), HER3 (*erb* B-3), and HER4 (*erb* B-4) (Yarden, 2001), as seen in Figure 1. The receptors are composed of three main structural domains: an extracellular region, a transmembrane segment, and a cytoplasmic portion (Hong & Ullrich, 2000). The extracellular domain acts to bind the different epidermal growth factor (EGF) ligands and is made up of two cysteine-rich domains (Hong & Ullrich). The transmembrane structure is a lipophilic region that anchors the receptor to the cell membrane. The intracellular portion of the receptor contains a tyrosine kinase domain and docking sites for additional kinase substrates (Hong & Ullrich). EGFs and their transmembrane receptor kinases play important cellular roles in normal and malignant cells, including cellular proliferation, survival, migration, and differentiation (Yarden). EGFR tyrosine kinase (EGFR-TK) is responsible for activating multiple downstream signaling pathways and has been shown through clinical trials to govern several aspects of tumor growth.

Wells (1999) was one of a number of authors to identify the seven genetically distinct ligands capable of binding with the EGFR. A ligand is a molecule, such as an antibody, hormone, or drug, that binds to a receptor. The seven distinct ligands are EGF, transforming growth factor alpha, heparin-binding EGF, amphiregulin, betacellulin, epiregulin, and neuregulin G2beta. The ligands, when bound to the extracellular receptor, can trigger *erb* B receptor aggregation or the formation of receptor heterodimers or homodimers and internalization (Yarden, 2001).

EGFR signal transduction occurs in normal and abnormal cells and is the result of a receptor being bound by a ligand. In normal cells, it is a multistage process. A ligand binds to the extracellular domain, inducing the receptor to dimerize (Hong & Ullrich, 2000). Dimerization that occurs between two molecules of the same receptor is known as homodimerization; between two molecules of different EGFRs, it is referred to as heterodimerization (Hong & Ullrich). Once dimerization occurs, the "circuit" is complete and the signal relayed.

EGFRs are widely expressed by many cell types, including those of epithelial and mesenchymal origin (Wells, 1999). Their biologic effects range from mitogenesis to apoptosis and migration to differentiation to dedifferentiation, even in the same cell, depending on the signaling pathway activated (Wells).

EGFRs are overexpressed on malignant cells and can stimulate tumor growth through the promotion of proliferation, angiogenesis, invasion, metastasis, and inhibition of apoptosis. Significant variation in overexpression and downregulation (or underexpression) has been identified in a number of malignancies.

EGFR expression has been reported to be downregulated in 33%–50% of human epithelial tumors (Harari, 2004; Mendelsohn, 2001). The variation may be a result of the

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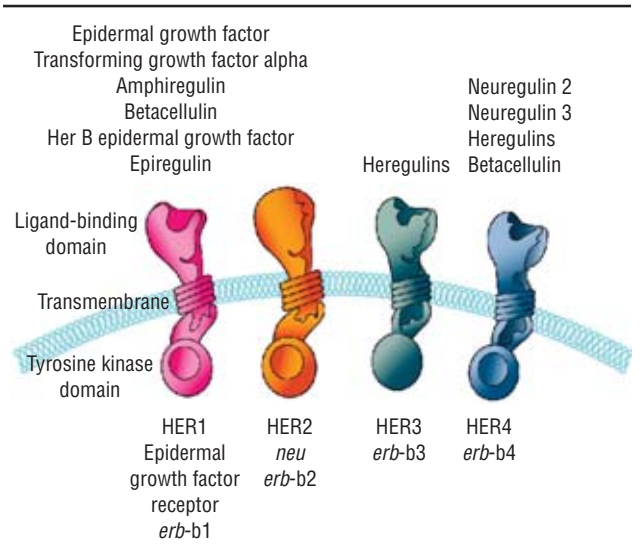

Figure 1. Epidermal Growth Factor Receptor Family

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methods used to measure the levels of EGFR expression. Overexpression of EGFR has been found on the most common types of nonepithelial malignancies, including cervical, uterine, colon, esophageal, ovarian, pancreatic, and renal cell cancers; glioma; and non-small cell lung cancer (NSCLC) (Harari).

Nicholson, Gee, and Harper (2001) reported on a retrospective review of more than 200 studies published from 1985–2000 and totaling more than 20,000 patients to determine whether EGFR overexpression could predict either recurrence-free or overall survival rates when compared with normal cellular EGFR expression. Ten tumor types provided enough data to be analyzed. Nicholson et al. reported that, in some cases, overexpression of EGFR correlated with decreased survival. The strongest correlation (70% of 74 studies) was observed in studies that involved participants with head and neck, cervical, ovarian, bladder, and esophageal malignancies. Other malignancies did not correlate as well. Fifty-two percent of studies involving gastric, breast, endometrial, and colon cancers showed an inverse correlation between EGFR overexpression and decreased recurrence-free and overall survival. Only 30% of studies involving patients with NSCLC demonstrated the correlation. The correlations were based on the cellular levels of EGFR and not the activated form of the receptor; as a result, underestimation of the effects of overexpression of EGFR may have occurred. Unfortunately, high levels of EGFR expression do not predict response to therapy. Several factors are known to affect tumor response, including mutations of the receptor, heterodimerization, and increased expression of ligands (Harari, 2004). Therefore, accurately predicting patient clinical responses to the agents can be difficult.

One method of targeting malignant cells is through the use of monoclonal antibodies. Kohler and Milstein (1975) first described the laboratory technique for mass production of antibodies directed at specific targets on cancer cells. Since then, many clinical trials have been initiated with naked and conjugated monoclonal antibodies, directed at various targets with a range of effectiveness. The antibodies can function by being directed against extracellular binding sites, preventing the internalization of receptor-antibody complexes and inhibiting EGFR signaling pathways, as well as potentially stimulating an immunologic response in a patient.

Cetuximab is a chimeric, EGFR-inhibiting, commercially available monoclonal antibody that is available for clinical use. It was approved in February 2004 for the treatment of irinotecan-refractory advanced metastatic colorectal cancer (U.S. Food and Drug Administration [FDA], 2005a). Other monoclonal antibodies that target EGFR inhibition include ABX-EGF, EMD 72000, MDX-447, h-R3, and MAB 806.

Another EGFR inhibitor pathway is through the inhibition of tyrosine kinase. The kinases are known to be signaling molecules that control many aspects of cell behavior, including cell proliferation, by determining when cells divide and how rapidly they do so. If the kinases are abnormally active, tumor growth is promoted.

Tyrosine kinase inhibitors are synthetic, mainly quinazoline-derived, low-molecular-weight molecules that interact with the intracellular tyrosine kinase domain of several receptors, including EGFR, and inhibit ligand-induced receptor phosphorylation by competing for the intracellular Mg-ATP binding site, thus preventing tyrosine kinase activation and inhibiting EGFR signaling (Harari, 2004). Gefitinib (Iressa™, Astra Zeneca Pharmaceuticals, LP, Wilmington, DE) and erlotinib (Tarceva™, OSI-774, Genentech, Inc., South San Francisco, CA) are the two commercially available tyrosine kinase inhibitors.

Gefitinib, formally known at ZD 1839, was approved by the FDA in May 2003 for the treatment of patients with NSCLC who had failed two or more courses of chemotherapy. Because gefitinib was approved through the accelerated program, clinical studies continued; in December 2004, the FDA announced that a clinical trial involving gefitinib failed to demonstrate a survival benefit for patients taking the drug when compared with those receiving placebo. The original 2003 approval had been granted based on a reported 10% response rate (complete response/partial response/stable disease) in patients taking the agent. At the time, that was considered a likely survival benefit. Under the accelerated approval program, a drug may be removed from the market if ongoing trials fail to show benefit. The FDA is deciding whether gefitinib will remain available commercially or be removed from the market. In a December 2004 communiqué, the FDA determined gefitinib to be an active agent in NSCLC, but as other, more active agents become available, gefitinib may be removed from the market. Interestingly, two subpopulations appear to achieve a better response to gefitinib: Asians and those who never have smoked. The reason is unclear. In the future, the use of gefitinib may be restricted to such subgroups of patients with NSCLC (FDA, 2004). Ongoing clinical trials with gefitinib have shown benefit in patients with pancreatic cancer, and objective responses have been documented in patients with ovarian and head and neck cancers.

Erlotinib hydrochloride received FDA approval in November 2004 for the treatment of locally advanced or metastatic NSCLC and is indicated for patients whose cancer has continued to progress despite other treatments, including at least one prior chemotherapy regimen (FDA, 2005b).

Other tyrosine kinase inhibitors in clinical trials include CI-1033, EDB-569, GW 2016, and PKI-166.

Vascular Endothelial Growth Factor

Angiogenesis is another targeted pathway. The process of angiogenesis has been recognized for more than 70 years, yet only in the recent past have researchers been able to demonstrate its efficacy clinically. Knowledge of the angiogenic process is being revised continually, with the greatest amount of information being gained since the 1970s. The entire cascade of events has been described as proliferation, migration and invasion of endothelial cells, organization of endothelial cells into functional structures followed by the maturation of vessels, and vessel regression (Hicklin & Ellis, 2005). The major pathway for the process to occur is via a family of proteins known as VEGF (see Figure 2).

Angiogenesis is defined as the formation of new blood vessels from existing vasculature. This differs from vasculogenesis, which describes the formation of larger blood vessels during embryonic development. The term angiogenesis is derived from two Greek terms: *angeion,* meaning vessel, and *genesis,* meaning birth. The formation of new blood vessels is an important aspect of disease development, not only in cancer but also in rheumatoid arthritis, asthma, cirrhosis, cardiovascular disease, and diabetic retinopathy. Normally, angiogenesis occurs in pregnancy, during the female reproductive cycle, and during wound healing and tissue repair. Other than these examples, the vasculature is relatively quiescent.

In tumors, a shift occurs in the homeostatic balance of proangiogenic and antiangiogenic factors, favoring the proangiogenic factors. The reason for this is survival. Much research has documented that oxygen can diffuse only 150–200 micromillimeters across capillaries. Therefore, if a tumor mass is to exceed one millimeter in any dimension, extensive vascularization must occur. If no oxygen supply is available, tumor cells will die. Prior to the actual growth of new blood vessels, angiogenic ligands pour into the microcellular environment and act on the various receptors. This process is called neovascularization (Ellis, 2004b). The entire process of neovascularization is complex, requiring multiple stimuli to act on the vasculature. Growth factors, cytokines, enzymes, lipids, and proteins, all generated by a tumor, stimulate growth and proliferation, forming new capillary structures (Ellis, 2004b). The resulting vasculature differs greatly from normal vessels in structure, order, and function. Angiogenesis is important for a tumor because it supplies not only oxygen but also nutrients, growth factors, hormones, proteolytic enzymes that influence hemostatic factors, and control of the coagulation and fibrinolytic system, as well as dissemination of tumor cells to distal sites (Hicklin & Ellis, 2005). The angiogenic process has been described as complex and multifactorial, involving numerous growth factors. VEGF, also known as vascular permeability factor, and other cytokines such as interleukin-8, fibroblast growth factor, and angiopoietins and their respective receptors (Ellis, 2004b) are examples of the growth factors. Hicklin and Ellis reported that increased tumor vascularization, with increased microvessel density and tumor expression of proangiogenic factors, has been associated with advanced tumor stage and poor prognosis in a variety of human cancers.

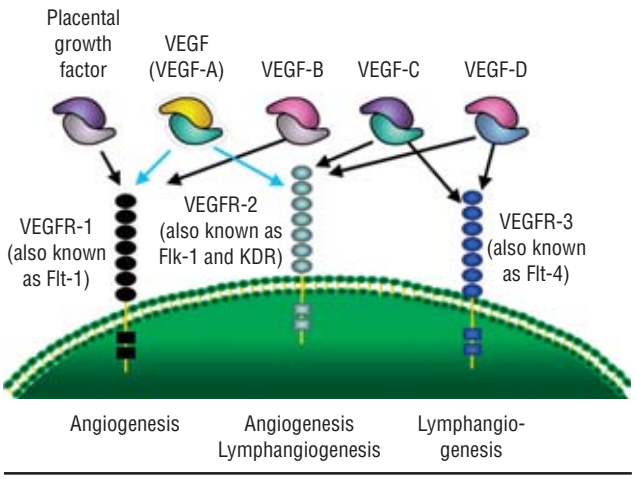

Figure 2. The Vascular Endothelial Growth Factor (VEGF) Family and Its Receptors

VEGFR—vascular endothelial growth factor receptor

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The VEGF family of angiogenic and lymphangiogenic growth factors is comprised of six secreted glycoproteins referred to as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). VEGF-A, called vascular permeability factor, was the first to be identified and is the best described (Dvorak, Brown, Detmar, & Dvorak, 1995). It is about 50,000 times more potent than histamine in allowing proteins to diffuse into the interstitium (Dvorak et al.). VEGF-A is essential for the stimulation of endothelial cell proliferation and is a survival factor for endothelial cells of newly formed blood vessels (Ellis, 2004b). VEGF production by a tumor may be initiated by tumor mutations governing a growth regulating pathway and by environmental conditions in the tumor (Ellis, 2004a). Hypoxia has been noted to be the most important environmental condition for inducing tumor cell VEGF-A production (Ellis, 2004b).

VEGF-B has been described as structurally close to VEGF-A. It normally is produced in large quantities by developing myocardium, fat, muscle, bone, pancreas, adrenal glands, and the smooth muscle cells of several large vessels (Ellis, 2004b). Ellis (2004b) further reported that VEGF-B might be an autocrine factor for tumor cell activation.

VEGF-C and D also are reported to play a role in new blood vessel growth, especially during tumor growth and other pathologic states (Ellis, 2004b). However, Hicklin and Ellis (2005) reported that their role in tumor angiogenesis is unclear. VEGF-E, as reported by Hicklin and Ellis, is not a mammalian VEGF homolog. Placental growth factor was discovered in the human placenta but has been detected in the heart, lungs, thyroid gland, skeletal muscles, and several tumors (Ellis, 2004a).

VEGF ligand activity is mediated via a group of receptors known as VEGF receptor (VEGFR) tyrosine kinases (Ellis, 2004a). The tyrosine kinase receptors have been designated as VEGFR-1 (also known as Flt-1), VEGFR-2 (also known as KDR and Flk-1 in humans), and VEGFR-3 (Flt-4). The receptors have overlapping and independent roles in vascular development and maintenance (Ellis, 2004a).

VEGFR-1 is critical for physiologic and developmental angiogenesis (Hicklin & Ellis, 2005). It also has been reported to function in the reduction and modulation of endogenous VEGF or PlGF activity. It has been shown to be present in the serum and amniotic fluid of pregnant women and in cycling human endometrium (Hicklin & Ellis). It also has been found in breast cancers and astrocytic tumors (Hicklin & Ellis).

VEGFR-2 is reported to mediate the majority of downstream effects of VEGF-A in angiogenesis. These downstream effects include alteration in microvascular permeability, endothelial cell proliferation, invasion, migration, and survival (Hicklin & Ellis, 2005).

VEGFR-3 is a receptor tyrosine kinase that originally was cloned from a human cell line and human placenta (Hicklin & Ellis, 2005). The factor has been reported to be expressed throughout the embryonic vasculature, but during development and in adulthood, its expression is limited to lymphatic endothelial cells (Hicklin & Ellis). In the normal physiologic mechanisms, VEGFR-3 is correlated with transient lymphangiogenesis in wound healing. It also is believed to play multiple roles in assisting cardiovascular development and remodeling in the primary vascular networks during embryogenesis. In adults, it has been reported to facilitate lymphangiogenesis. Its role in cancer is unclear, but it has been observed in patients with breast cancer and melanoma. Detectable VEGFR-3 levels and increases in VEGF-C and VEGF-D have been associated with lymph node metastasis. Hicklin and Ellis reported that inhibition of VEGFR-3 signaling has been shown to decrease tumor lymphangiogenesis and lymph node metastasis.

Neurolipin 1 and 2 may serve as coreceptors for VEGF, suggesting that they have a role in angiogenesis (Hicklin & Ellis, 2005). Their specific functions in regard to vessel development and angiogenesis are not known.

When VEGF is activated, whether by normal or malignant cells, it triggers cellular signaling that alters endothelial cell survival, mitogenesis, migration, differentiation, vascular permeability, and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation (Hicklin & Ellis, 2005).

VEGF is essential for the growth and proliferation of malignant cells. Overexpression of VEGF has been associated with poorer prognosis in certain malignancies, including colorectal, gastric, pancreatic, prostate, and lung cancers and melanoma (Hicklin and Ellis, 2005). In addition, malignant effusions are associated with increases in vessel permeability mediated by VEGF (Hicklin and Ellis).

The use of angiogenesis inhibitors has been the subject of numerous clinical investigations since the 1980s. As the VEGF pathway was recognized as a key regulator of angiogenesis, it provided a target for multiple inhibitory strategies. Neutralizing antibodies to VEGF or VEGFR, soluble VEGF and VEGFR ligands, and tyrosine kinase inhibitors to VEGFRs (Hicklin & Ellis, 2005) are just a few of the ways to inhibit VEGF. The current VEGF/VEGFR inhibitors under clinical investigation as reported by Hicklin and Ellis are IMC-1121 B, CDp-791, 2C3, PTK-787, AEE 788, ZD 6474, AZD 2171, SU 11248, AG 13925, AGO 13736, CEP 7055, CP-547, 632, VEGF-TRAP, GW 786024, Bay 93-4006, and AMG 706.

Bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA) is the one angiogenesis inhibitor currently approved by the FDA. Bevacizumab's current indication is in combination with 5-fluorouracil (5-FU)–based chemotherapy as first-line therapy in patients with metastatic colorectal cancer. Bevacizumab is a recombinant humanized monoclonal antibody directed toward VEGF that blocks the binding of the ligand VEGF-A, commonly known as VEGF, blocking its ability to activate the receptor on endothelial cells, thereby inhibiting the growth of new blood vessels (Hoff, 2004). This action has two proposed consequences. The first is that the agent inhibits the growth of new vessels and induces the regression of existing vessels, and the second suggests that bevacizumab lowers the interstitial pressure, altering tumor vasculature and improving oxygenation, resulting in tumor shrinkage (Genentech, Inc., 2004).

In the mid-1990s, D'Amato, Loughnan, Flynn, and Folkman (1994) recognized thalidomide (Thalomid™, Celgene, Summit, NJ) as having antiangiogenic properties that correlated with its well-known teratogenic effects. The pharmacokinetics are extremely complex, and the mechanism by which it exerts its antiangiogenic affect is not understood completely. The anticancer effects reported by Kumar, Witzig, and Rajkumar (2004) confirmed that thalidomide is a potent angiogenesis inhibitor. Clinical studies have shown that thalidomide can decrease vascular density in granulation tissue, have both antitumor necrosis factor alpha and immunomodulatory effects, and affect cellular adhesion molecules (Kumar et al.).

Nursing Implications

As knowledge about targeted therapy has progressed, information about unique and classic side effects has been described. Nurses are in a key position to assess and intervene as adverse effects present in patients receiving targeted therapy.

The most common side effects associated with the EGF inhibitors cetuximab, gefitinib, and erlotinib include skin rash, fatigue, nausea, vomiting, stomatitis, and diarrhea. Because cetuximab is a monoclonal antibody, it has the added side effect of hypersensitivity reaction. Gefitinib and molecule tyrosine kinase inhibitors share the same side-effect profiles of interstitial lung disease (reported in about 1% of patients), nausea, vomiting, asthenia, diarrhea, visual ocular changes, and skin reactions.

Most nurses are comfortable addressing the more common side effects of the agents, as well as hypersensitivity reactions. The unique reaction of interstitial lung disease is not part of the usual side-effect profile. Because interstitial lung disease occurs rarely, nurses are less familiar with its signs and symptoms. Usually a patient complains of cough, dyspnea, and low-grade fever (Wilkes & Barton-Burke, 2005). Because the symptoms are nonspecific, nurses must be vigilant to assess patients carefully at each visit so that early interventions can occur.

Although skin rashes are common side effects of chemotherapy, the rashes seen as a side effect of EGF inhibitors are more severe. Generally, the rashes are erythematous and acneiform in appearance; usually involve the face, neck, arms, and upper torso; and usually cover less than 50% of the body. Data suggest that a correlation can be made between the development of a rash and clinical response that can be attributed to EGFR-TK inhibition in the skin (Krozely, 2004).

Nursing interventions may include using mild soap and water to keep areas clean. Topical agents such as diphenhydramine lotion, Aveeno™ body wash (Johnson and Johnson Inc., Fort Washington, PA), and Curel (Andrew Jergens Company, Cincinatti, OH) have been reported to provide symptomatic relief for some patients (Krozely, 2004; Pizzo, 2004). Those with more severe rashes may require topical clindamycin, antibiotic ointment, or systemic antibiotics. A rash should be assessed appropriately to determine proper interventions

and to document improvement or progression. Many patients have required discontinuation or a drug holiday because of the severity of the rash (personal communication, A. Venook, April 4, 2005).

A number of side effects of bevacizumab have been described. Common side effects reported at the time of approval were systolic hypertension, proteinuria, and low-grade infusion-related reactions (Iqbal & Lenz, 2004). Severe side effects that were described at the time of FDA approval were intratumor bleeding, pulmonary emboli, and peripheral vascular thrombosis (Iqbal & Lenz). In addition, gastrointestinal perforations have been reported since bevacizumab became commercially available (Franson & Lapka, 2005).

More recently, adverse events have been reported with greater frequency and increased severity. Cerebrovascular accidents and stroke, myocardial infarctions, transient ischemic attacks, and angina (Iqbal & Lenz, 2004) are examples of such adverse events. The population noted to be most at risk for such severe side effects are patients who have had a history of thromboembolic disease prior to receiving bevacizumab therapy and those older than 65 years (Iqbal & Lenz).

Common interventions for the most frequent side effect, hypertension, include angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers (Genentech, Inc., 2004). Traditional nursing interventions of close blood pressure monitoring while a patient is receiving the agent and tracking changes in blood pressure should be standard. Dietary modifications and lifestyle changes such as stress reduction and exercise also should be incorporated. Patients receiving bevacizumab also should be counseled to decrease alcohol intake (Franson & Lapka, 2005). Proteinuria was reported in patients participating in clinical trials (Genentech, Inc., 2004). Interventions for proteinuria include hydration and nutritional assessment (Franson & Lapka).

Infusion reactions have been reported at a rate of less than 3%; therefore, the manufacturer does not recommend premedications (Genentech, Inc., 2004). Nurses should be aware of this small risk and have appropriate emergency equipment available if necessary. Emergency supplies usually include medications such as diphenhydramine, epinephrine 1:1000, hydrocortisone, and oxygen to be delivered with an ambulatory bag valve mask resuscitator if necessary. For repeat infusions in patients who previously have experienced mild infusion reactions, prophylactic medications such as diphenhydramine and an H_2 antagonist are appropriate, as is lengthening infusion time (Franson & Lapka, 2005).

Perforations and thromboembolic events have been reported rarely, but nurses should be aware of the possibility. Interventions include the close monitoring of any patient with a history of unusual bleeding or clotting. Patients who have had prior history of thromboembolic events and have received anticoagulation therapy also should be followed closely. Ignoffo (2004) reported that warfarin has an enhanced effect when administered with 5-FU, and using 5-FU plus bevacizumab may increase bleeding risk. Patients should be instructed to monitor incision lines for change in color and increase in size and also monitor any increase in abdominal pain. Other sources of bleeding such as epistaxis, bleeding gums while brushing or flossing teeth, and changes in the color of urine or stool should be reported immediately.

Individuals at increased risk of embolic phenomena should be instructed to seek medical attention for any signs or symptoms of myocardial infarction, pulmonary emboli, cerebral vascular accident, or deep vein thrombosis, including chest pain, arm or jaw pain, profuse diaphoresis, changes in respiratory pattern such as shortness of breath, increased difficulty breathing with exertion, leg pain, swelling, or erythema (Ignoffo, 2004).

All targeted agents require close monitoring of patients. Nurses, as part of the interdisciplinary team, have a significant role to play in patient education, assessment, and intervention. Patients usually approach nurses with their questions, symptoms, and concerns.

Summary

Molecular targeting of receptors and pathways has shown promise, and researchers had hoped that the ability to isolate and attack a unique receptor or cellular process would lead to a cure for cancer, or at least convert cancer to a chronic disease. Unfortunately, that has not been the case. Clearly, this is a treatment form in its infancy, with much still left to understand. Many more agents in clinical trials and many cellular interactions need further research. In addition, the problem of resistance also will need to be addressed. Combining more than one molecularly targeted agent may be required to achieve the best response and avoid resistance, just as combination chemotherapy was shown to be more effective compared to single-agent chemotherapy.

Targeted therapies are beginning to have a place in cancer therapy. As additional agents are approved, their positions in the arsenal for the treatment of cancer will become more prominent. Nurses play a major role in the care and treatment of patients with cancer. As such, nurses would be prudent to learn all there is to know about this new approach to treating malignancies. Targeted therapies may be one of many keys that unlock the secret of cancer; if so, nursing will be standing at the door.

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