Anti-Angiogenic Drugs: Involvement in Cutaneous Side Effects and Wound-Healing Complication

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Significance: The uses of anti-angiogenic drugs have not only made an impact on the battle to eliminate cancer but are also responsible for a number of medical complications. The long-term use of these drugs has increased the spectrum and incidence of cutaneous side effects and wound-healing complications. It is, therefore, necessary to understand the overall impact that these drugs have on patient care.

Recent Advances: This review highlights the role of vascular endothelial growth factor and fibroblast growth factor in angiogenesis and wound healing and looks at how angiogenic inhibitors promote wound-healing complications.

Critical Issues: With an increased use of anti-angiogenic drugs for the treatment of various cancers and ocular diseases, there is an increased need for clinicians to define the risks and to optimize the usage of these drugs to reduce the incidence of cutaneous side effects and wound-healing complications. In addition, awareness is needed when treating patients on anti-angiogenic drugs so as not to exacerbate potential wound-healing complications when performing surgical procedures.

Future Directions: Clinicians and surgeons will need to develop management guidelines to optimize patient care to reduce the risk of morbidity. When performing a surgical procedure, the impact of adverse effects from the use of anti-angiogenic drugs should be considered to ensure the welfare of the patient. In addition, the development of more specific inhibitors is necessary to reduce target effects to reduce the occurrence of adverse effects.

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SCOPE AND SIGNIFICANCE

SINCE THE USE of anti-angiogenic drugs such as bevacizumab (Avastin; Genentech), ranibizumab (Lucentis; Genentech), and sorafenib (Nexavar; Bayer) are becoming more common in the treatment of cancer and retinal diseases, the incidence of cutaneous side effects and wound-healing complications will increase. Thus, it is important for clinicians to have an understanding of the serious toxicities of these drugs. In addition, surgeons and clinicians should be cognizant of the potential wound-healing complications that may arise when considering surgical proce-

dures on patients being administered anti-angiogenic drugs. This review provides a basic understanding of anti-angiogenic drugs and the role they play in modulating wound healing.

TRANSLATIONAL RELEVANCE

The concept of inhibiting angiogenesis as a therapeutic for treating diseases such as cancer has been around since the 1970s when Judah Folkman proposed that cancer growth is dependent on blood vessel growth or angiogenesis.¹ Targeting angiogenesis was thought to have

minimal side effects due to the quiescent nature of the vasculature in adults. The development of antibodies and small-molecule inhibitors of vascular endothelial growth factor (VEGF) and its receptor have been successfully used in the treatment of a number of cancers and ocular diseases. Extended use of anti-angiogenic drugs has led to an increased incidence in wound-healing complications. Thus, better inhibitors are needed to reduce the incidence of wound-healing complications due to long-term usage.

CLINICAL RELEVANCE

Currently, there are ~17 FDA-approved anti-angiogenic drugs that are used for the treatment of cancer and ocular disease. The increased use and duration of administration has heightened the adverse reactions and toxicities of these drugs. The extended use (years) of these drugs has increased the incidence of wound-healing complications. Clinicians should be aware of the use of these drugs to successfully manage the potential incidence of wound-healing complications due to surgical procedures. Therefore, appropriate management of these drugs and knowledge of drug toxicities become important for limiting the risk of wound-healing complications in high-risk patients (high risk of developing ulcers) and those requiring surgery. The development of guidelines is necessary to successfully manage wound-healing complications in those patients being treated with anti-angiogenic drugs. In addition, clinicians have to be aware of these potential side effects when performing surgery on these patients.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Wound healing and angiogenesis

Wound healing is a process of cascading events that involves cellular, humoral, and molecular mechanisms to repair damaged tissue. It can be divided into four distinct but overlapping phases.² The first phase is clot formation (coagulation phase), which occurs in seconds to minutes and is triggered via the intrinsic (blood) or extrinsic (tissue) coagulation pathways. This phase is dedicated to hemostasis. The activated platelets release clotting factors, cytokines, and growth factors that promote constriction of the injured vessels and clot formation to stop blood loss.³

Activation of the inflammatory process is the 2nd phase, which occurs in hours and lasts for days. The formation of a provisional matrix, composed mainly of fibronectin and fibrin, occurs

within hours during the inflammatory phase to provide a scaffold for the immigration of endothelial cells, epithelial cells, fibroblasts, and leukocytes. Early in the phase, neutrophils are activated and are responsible for the elimination of bacteria and necrotic tissue. Around day 3, activated macrophages are recruited to the wound site to remove pathogens and cellular debris. The macrophages release cytokines and growth factors to promote re-epithelialization and wound contraction. The inflammatory phase is essential for the initiation of wound closure and tissue repair.

At day 3, the start of the granulation phase (3rd phase), angiogenesis begins to occur to establish a new vascular network, granulation tissue forms, and wound re-epithelialization is occurring. During this phase, a new vasculature is established to provide oxygen and nutrients to the wound site. At this time, the fibronectin/fibrin matrix of the clot is degraded and replaced by collagen III by activated myofibroblasts.⁴

In the last phase (remodeling), the nascent vasculature regresses significantly; the provisional matrix is degraded and replaced by collagen I, metabolic activity slows to a stop, and epithelial cells differentiate back to keratinocytes. The remodeling phase will start to occur around day 21 and can last for a year or longer depending on location and severity. Myofibroblasts are responsible for the rearrangement of the collagen into linear bundles to increase tensile strength and proteoglycan deposition to increase wound resilience to deformation. At this stage, there is a decrease in angiogenic factors and an increase in the secretion of anti-angiogenic factors, such as IP-10. The nascent vascular undergoes significant pruning to reduce the excessive vascularization of the wound tissue. The reduction in the new vasculature is necessary to enhance tensile strength of the new tissue. An absence of vascular regression causes the wound tissue to be weaker and may promote hypertrophic scar formation.⁵ Thus, excessive vascularization causes a significant reduction of cutaneous wound tensile strength, leading to a weakening of the regenerated tissue.

Angiogenesis. Angiogenesis is the formation of new blood vessels from the existing vasculature. Physiological angiogenesis in adults occurs under limited circumstances: the female reproductive cycle, organ growth, and wound healing. On the opposing end, angiogenesis is a major contributing factor in disease progression. It plays an essential role in pathologies such as tumor growth, ocular diseases, endometriosis, psoriasis, and rheumatoid

arthritis. Pathological angiogenesis has been implicated in more than 80 diseases, and, thus, it is a target for therapeutic intervention.

Angiogenesis occurs with the stimulation of endothelial cells by angiogenic factors.⁶ Some of the most abundant and potent angiogenic factors are growth factors, which include VEGF, fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and hepatocyte growth factor.⁶ In addition to these growth factors, there are a number of cytokines and small molecules that promote angiogenesis. Growth factor stimulation of endothelial cells induces cell migration and proliferation, capillary tube morphogenesis, vascular remodeling, and maturation.

Angiogenesis during wound healing. During the granulation phase, an excess of angiogenic factors is released, prompting a vigorous angiogenic response and resulting in a nascent vasculature which surpasses that of normal tissue.⁷ This neovasculature provides a conduit for nutrients, tissue oxygenation, and cell trafficking to facilitate wound closure and tissue regeneration. During the remodeling phase, the majority of the nascent vessels regress and the vessels within the wound are pruned to a density similar to unwounded tissue. A disruption in this process or inadequate angiogenesis can lead to a delay or disruption of the wound-healing process. Inadequate vessel formation is a major factor in the development of non-healing wounds.⁷ The development of chronic wounds due to inadequate vascularization is evident in people with diabetes, venous disorders and in the aged.

Recent studies have demonstrated that a reduction in the angiogenic response is still able to facilitate normal skin healing.^{8,9} The use of anti-angiogenic agents at low doses, which reduced the level of vessel formation but did not eliminate angiogenesis, demonstrated normal healing of the skin.⁹ This observation is found under physiological conditions in the oral mucosa. Wounds in the mucosa are known to heal rapidly and to exhibit a less angiogenic response than the skin.¹⁰ In addition, scarless wound healing is found to have a reduced angiogenic response.⁸ One explanation is that many of the vascular structures formed during the granulation phase are not functional.¹¹ These vessels have been found to be immature and highly permeable.¹² Similar vessels have been observed in the vasculature around tumors. The bolus of angiogenic factors being secreted by the inflammatory cells may prevent the neovasculature from

progressing to a mature state. Therefore, partially blocking angiogenesis without significantly affecting vessel development may not, to a degree, interfere with the wound-healing process. These studies may indicate that a short administration of a low dose of anti-angiogenic agents may not interfere with the wound-healing process.

Angiogenic molecules

There are a number of molecules that can promote angiogenesis. These molecules can be classified into different groups, which include growth factors, cytokines, matrix proteins, phospholipids, ribonuclease, and glycoproteins. These molecules promote angiogenesis by stimulating endothelial migration and proliferation. Alone, these factors can stimulate angiogenesis but they are not able to facilitate complete angiogenesis. Vessel stabilization and maturation is a function of a number of angiogenic factors acting on endothelial cells at various times during angiogenesis to promote a functional vessel. VEGF and FGF are two of the most potent angiogenic factors, and they play a significant role in angiogenesis and vessel maturation. VEGF is secreted by a number of tumors and is important in the formation of tumor vasculature. Thus, inhibition of VEGF and its receptor has been the primary focus for the development of novel anti-cancer therapies. Inhibition of the VEGF pathway has been the primary focus for inhibiting tumor angiogenesis.

It is well established that FGF acts synergistically with VEGF to promote vessel growth and maturation. FGF has gained significant attention over the past decade given its role in multiple cellular processes. In addition to promoting angiogenesis, aberrant FGF promotes tumor growth and survival, making it a compelling target as a therapeutic for cancer intervention. In wound healing, FGF is a major player in the inflammatory phase and is a key factor in promoting fibroplasia in the granulation phase. The development of agents targeting the FGF pathway and possible use with anti-VEGF therapies further enhances the need for clinicians to optimize the care provided to patients undergoing anti-angiogenesis treatments to reduce wound-healing complications.

VEGF. The VEGF family contains six known members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). VEGF is one of the most prevalent and potent inducers of angiogenesis and is produced by a number of cells, including fibroblasts, macrophages, lymphocytes, platelets, and epithelial cells.¹³ It is

one of the main factors promoting angiogenesis in wound healing.¹⁴ VEGF expression is also up-regulated in pathological angiogenesis and plays a significant role in cancer and ocular disease.^{15,16} VEGF stimulates endothelial migration, proliferation and acts as a survival factor by inducing the expression of antiapoptotic factors (Fig. 1).^{17,18} In addition to its angiogenic activities, it provides survival signals for neurons, promotes inflammatory cell chemotaxis, and recruits endothelial progenitor cells.

VEGF-A is the most prevalent member of the family and is usually referred to as VEGF in the context of angiogenesis. Human VEGF-A exists as four isoforms as a result of alternative exon splicing: VEGF₁₂₁, VEGF₁₆₅, VEGF₁₈₉, and VEGF₂₀₆ amino acids.¹⁹ These isoforms differ in their biological properties. VEGF₁₆₅, VEGF₁₈₉, and VEGF₂₀₆ bind to heparin and heparin-sulfate proteoglycans. These isoforms are typically found

bound to the extracellular matrix or cell membrane. Loss of heparin binding through plasmin cleavage results in diminished mitogenic activity.¹⁹ VEGF₁₂₁ lacks the heparin-binding motif and is the only isoform that is diffusible.¹⁹ VEGF₁₆₅ is the most dominant of the isoforms *in vivo*. Loss of these isoforms has shown dramatic effects on vessel formation. In animal studies, knocking out VEGF₁₆₅ and VEGF₁₈₉ demonstrated vessels with fewer branches and larger lumens that were leaky and unstable.¹⁹ In addition, knocking out VEGF₁₂₁ leads to more branching of the vessels.¹⁹

VEGF receptor. There are three main isoforms of the VEGF receptor (VEGFR), which are numbered VEGFR1 (Flt-1), VEGFR2 (Flk-1, KDR), and VEGFR3 (Flt4). VEGFR1 and VEGFR2 are expressed on vascular endothelial cells and play a significant role in regulating angiogenesis.²⁰ VEGFR3 is expressed on lymphatic endothelial

Figure 1. VEGF signaling pathways. VEGF activation of VEGFR sets into motion a complex network of intracellular signaling pathways that promote migration, proliferation, survival, and permeability. Activation of FAK and FYN promotes migration. Proliferation is through the activation of PLC- γ and GRB2-SOS. Production of nitric oxide (NO) and prostaglandins induces vascular permeability. Activation of AKT inhibits the apoptotic proteins Bad and caspase-3. AKT, protein kinase B; GRB2, growth factor receptor-bound protein 2; PLC- γ , phospholipase C- γ ; SOS, son of sevenless; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

cells and mediates lymphangiogenesis.²⁰ VEGFR2 is the main receptor on endothelial cells that signals an angiogenic response, and its primary ligand is VEGF-A.²⁰ It is primarily not only found on endothelial cells but is also expressed on monocytes,²¹ macrophages,²² and epithelial cells.²³ VEGFR2 activation induces signaling of the mitogen-activated protein kinase (MAPK) signaling cascade to stimulate proliferation and migration (Fig. 1). Activation of the PI3 kinase/protein kinase B (AKT) pathway promotes endothelial survival and vessel permeability (Fig. 1).

VEGFR1 binds VEGF-A with a higher affinity than VEGFR2. In addition, VEGF-B and PlGF have only been found to bind to VEGFR1.²⁰ VEGFR1 expression is found on multiple cell types, including fibroblasts,²⁴ macrophages,²⁵ monocytes,²⁶ and epithelial cells.^{27,28} VEGFR1 has been shown to have both positive and negative effects on angiogenesis.²⁰ More recent studies have demonstrated VEGFR1 as a positive regulator of endothelial migration, proliferation, and vessel stability.²⁰ The signaling cascade for VEGFR1 is not well understood but has been shown to activate the PI3K/AKT, p38 kinase, and extracellular signal regulated kinase (ERK) 1/2 pathways to promote cell survival and migration.²⁰ In nonendothelial cells, VEGFR1 plays a role in promoting migration, proliferation, and differentiation.^{29,30} Although VEGFR1 has been shown to play a role in angiogenesis, it does not seem to be required for endothelial function but has been found to play a relevant role in the activation of nonendothelial cells, in particular macrophages and epithelial cells. Thus, the effects of VEGF inhibition is not specific for endothelial cells but affects a number of cells involved in wound healing.

FGF. The FGF family currently contains 22 members. Of the members, FGF-1 (aFGF) and FGF-2 (bFGF) are important in the development of new blood vessels and play a major role in wound healing. FGF-2 has been found to be twice as potent as VEGF,³¹ promotes endothelial cell proliferation, migration, and plays a role in revascularization. In addition, FGF knockout mice showed a severe defect in wound healing.³² FGF-2 promotes mitogenesis of smooth muscle cells and fibroblasts, and FGF-1 is a potent stimulator of fibroblast activity. FGF-7 and FGF-10 stimulate proliferation, migration, and differentiation of epithelial cells. FGFs play an important role in the progression of the inflammation, granulation, and remodeling phases of wound healing. During inflammation, the release of FGF-1 promotes inflammatory cell migration. In the

granulation phase, FGFs act as proliferative agents on endothelial cells and fibroblasts and facilitate migration. FGF-7 promotes epithelial proliferation and differentiation to keratinocytes. Thus, FGFs are critical for proper wound healing.

FGF receptor. The FGF receptor (FGFR) family consists of four members FGFR1-FGFR4. Endothelial cells have been found to mainly express FGFR1 and have low expression of FGFR2. Currently, there are no reports of either FGFR3 or FGFR4 expression on endothelial cells. FGF-1 can bind to all four FGFR family members, where FGF-2 binds predominantly to FGFR1 and with less affinity to FGFR2. FGFR-1 signal transduction activates the phospholipase C- γ (PLC- γ), Shc, Ras, and MAPK signaling pathways (Fig. 2). PLC- γ activation promotes downstream activation of protein kinase C promoting cell migration. Shc activation further promotes migration. Activation of the Ras and MAPK pathways promotes proliferation.

Anti-angiogenic drugs

Angiogenesis plays a central role in tumor growth and metastasis, and, therefore, blockade has been viewed as an effective strategy for the treatment of tumor growth and progression. Judah Folkman was the first to suggest inhibition of angiogenesis as a therapeutic for the treatment of cancer.¹ Targeting angiogenesis for the treatment of cancer was initially proposed to exhibit minimal side effects due to the quiescent nature of the vasculature in adults. Since FDA approval of bevacizumab in 2004 for the treatment of metastatic colorectal cancer, the use of these drugs has expanded and is currently being used for the treatment of retinal diseases (*i.e.*, age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions). Thus, the use of anti-angiogenic drugs is being viewed as a viable option for the treatment of a variety of diseases where pathological angiogenesis is an underlying cause of the disease.

There are a number of current strategies for the inhibition of angiogenesis that include monoclonal antibodies, receptor antagonists, soluble receptors, and antisense mRNA. Currently, FDA-approved drugs for clinical usage for the treatment of specific cancers and retinal diseases are mainly monoclonal antibodies and small-molecule inhibitors of tyrosine kinase (Table 1). There is a vast pipeline of drugs in clinical trials awaiting FDA approval, suggesting that their use may become standard practice, thus increasing the need to be aware of

Figure 2. FGF signaling pathways. FGF-1 or FGF-2 activation of FGFR promotes migration and proliferation of endothelial cells, fibroblasts, and epithelial cells. Migration is through the activation of PKC, and proliferation is promoted by the activation of Ras-MAPK pathways. FGF, fibroblast growth factor; FGFR, FGF receptor; MAPK, mitogen activated protein kinase; PKC, protein kinase C.

Table 1. FDA-approved angiogenesis inhibitors

Inhibitor	Trade name (manufacturer)	Type of drug	Target	Clinical usage
Bevacizumab	Avastin (Genentech)	Monoclonal antibody	VEGFR1–2 tyrosine kinase	Metastatic CRC, NSCLC, glioblastoma, metastatic RCC
Cetuximab	Erbix (Bristol-Myers Squibb)	Monoclonal antibody	EGFR tyrosine kinase	Metastatic CRC, RCC
Panitumumab	Vectibx (Amgen)	Monoclonal antibody	EGFR	Metastatic CRC
Ranibizumab	Lucentis (Genentech)	Monoclonal antibody	VEGF-A	Wet age-related macular degeneration
Trastuzumab	Herceptin (Genentech)	Monoclonal antibody	HER2	Advanced RCC
Axitinib	Inlytan (Pfizer)	Small-molecule inhibitor	VEGFR1–3	Advanced RCC
Cabozantinib	Cometriq (Exelixis)	Small-molecule inhibitor	VEGFR2, c-Met	Metastatic medullary thyroid cancer
Erlotinib	Tarceva (Genentech)	Small-molecule inhibitor	EGFR tyrosine kinase	Advanced or metastatic NSCLC
Everolimus	Afinitor (Novartis)	Small-molecule inhibitor	mTOR, PI3/AKT pathway	Advanced RCC, pancreatic neuroendocrine tumor, SEGA
Imiquimod	Aldara (Medicis)	Small-molecule inhibitor	TLR-7	Actinic keratosis, basal cell carcinoma
Pazopanib	Votrient (GlaxoSmithKline)	Small-molecule inhibitor	VEGFR, PDGFR, c-Kit	Advanced RCC
Regorafenib	Stivarga (Bayer)	Small-molecule inhibitor	VEGFR1–3, PDGFR, FGFR, Kit, Raf, RET	Metastatic CRC,
Sunitinib	Sutent (Pfizer)	Small-molecule inhibitor	VEGFR1–3, PDGFR β , RET	Advanced RCC, GIST, pancreatic neuroendocrine tumor
Sorafenib	Nexavar (Bayer/Onyx)	Small-molecule inhibitor	VEGFR1–3, PDGFR β , Raf-1	Advanced RCC, advanced HCC
Temsirolimus	Torisel (Wyeth)	Small-molecule inhibitor	mTOR	Advanced RCC
Vandetanib	Caprelsa (AstraZeneca)	Small-molecule inhibitor	VEGFR, FGFR	Medullary thyroid cancer
Pegaptanib	Macugen (OSI Pharmaceuticals)	Pegylated aptamer	VEGF	Wet age-related macular degeneration

AKT, protein kinase B; CRC, colorectal cancer; EGF, epidermal growth factor; EGFR, EGF receptor; FGF, fibroblast growth factor; FGFR, FGF receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; mTOR, mammalian target of rapamycin; NSCLC, nonsmall cell lung cancer; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; RCC, renal cell cancer; SEGA, subependymal giant cell astrocytoma; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

the use of these drugs before initiation of surgical procedures and in patients who are at a high risk for the development of ulcers.

Anti-VEGF drugs. VEGF has been found to play a central role in the development of tumor vasculature³³; thus, it has been the focus of anti-angiogenesis drug development.³⁴ Current strategies focus on the inhibition of VEGF binding to its receptor (VEGFR) or inhibition of VEGFR downstream signaling molecules (Table 1). The first FDA approved drug was bevacizumab (Avastin), which is currently approved for use in the treatment of cancer (metastatic colorectal cancer, non-squamous nonsmall lung cancer, metastatic kidney cancer, and glioblastoma)³⁵ and age-related macular degeneration.³⁶ Bevacizumab is a recombinant humanized monoclonal antibody that is constructed to inhibit all VEGF isoforms, and it has not been found to recognize other growth factors.

Clinical studies have shown that VEGFR expression levels correlate with the development of tumor angiogenesis. This has led to the targeting of VEGFR tyrosine kinase activity. The majority of VEGFR inhibitors are small-molecule agents that inhibit receptor kinase function. These inhibitors possess advantages compared with the antibody-based strategies, because they can be taken orally versus an injection, diffuse more rapidly, and currently demonstrate less drug resistance. Of major concern with these compounds is target specificity (*i.e.*, inhibiting protein kinases of nontarget receptors) for acceptable side-effect tolerability. The two most commonly used FDA approved small-molecule inhibitors are sunitinib (Sutent) and sorafenib (Nexavar). Sunitinib has been approved for the treatment of renal cell carcinoma and gas-

trointestinal stromal tumor. It targets the protein tyrosine kinases of VEGFR, PDGFR, and c-Kit.³⁷ Sorafenib is approved for the treatment of hepatocellular carcinoma and renal cell carcinoma. It is a dual action inhibitor that targets the MAPK pathway in tumor cells and VEGFR and PDGFR in tumor vasculature.³⁸

Anti-FGF drugs. With the development of tumor resistance to anti-VEGF therapy, targeting FGF and its receptors may be an alternate treatment for cancer due to its role in tumor angiogenesis. In addition, FGF production has been implicated in tumor growth and metastasis.³⁹ The progression of a number of tumors, including prostate, colon, breast, and lung cancer, has been linked to over-expression of FGF. FGF secretion by the tumor is thought to be a contributing factor in tumor resistance to VEGF inhibitors. Recent animal studies using dual treatment of VEGF and FGF inhibitors were observed to be more efficacious than VEGF inhibition alone.⁴⁰

Identification of FGF having a defined role in tumor angiogenesis and growth has sparked the development of a number of FGF targeting agents (Table 2). Many of the FGF inhibitors also inhibit VEGFRs and PDGFRs. The ability of these inhibitors to target multiple angiogenic receptors may enable them to circumvent VEGFR inhibitor resistance. Of the current FGF inhibitors, vartegatef has shown the most success and is being evaluated in phase III trials.⁴¹ In phase I/II trials, vartegatef was found to have a very low incidence of vascular and dermatological side effects. Dovotinib showed lower incidence of dermatological effects but had disappointing results in phase II/II trials in breast, bladder, and renal cancers.⁴¹ Lenvantinib, which

Table 2. Fibroblast growth factor receptor inhibitors

Inhibitor	Trade name (manufacturer)	Type of drug	Target	Clinical trial	Clinical indications
IMC-A1	(ImClone)	Monoclonal antibody	FGFR1	Preclinical	
PRO-001	(Pro Chon Biotech)	Monoclonal antibody	FGFR3	Preclinical	
R3Mab	(Genentech)	Monoclonal antibody	FGFR3	Preclinical	
AB1010	Masantanib (AB Science)	Small-molecule inhibitor	FGFR3, PDGFR α , β	Preclinical	
AZD4547	(AstraZeneca)	Small-molecule inhibitor	KIT, TLLyn	I-II	Squamous NSCLC, gastric adenocarcinoma, solid malignant tumors
BGJ398	(Novartis)	Small-molecule inhibitor	FGFR1-4	I	advanced solid tumors with FGF-R alteration
BIBF1120	Vargatef (Boehringer-Ingelheim)	Small-molecule inhibitor	FGFR1-3, VEGFR1-3, PDGFR α , β	I-III	NSCLC, Metastatic CRC, advanced HCC
BMS 582664	Brivanib (Bristol-Myers Squibb)	Small-molecule inhibitor	Src, Lyn	I-II	advanced HCC
E7080	Lenvantinib (Eisai)	Small-molecule inhibitor	FGFR1-3, VEGFR1-3, PDGFR α , β	I-II	advanced HCC, melanoma, thyroid
TK1258	dovotinib (Novartis)	Small-molecule inhibitor	FGFR1, VEGFR1-3, PDGFR α , β	I-III	RCC, breast cancer, relapsed multiple myeloma, urothelial cancer
TSU-68	Orantinib (Taiho Pharmaceutical)	Small-molecule inhibitor	KIT	I-II	Multiple myelomas

has a higher affinity for VEGFR than FGFR, demonstrated similar side effects as observed with VEGFR inhibitors.⁴¹ Although these drugs are still in clinical trials, the potential of these inhibitors acquiring FDA approval increases with a higher incidence of tumor resistance to anti-VEGF therapy. FDA approval of FGF inhibitors may translate into an increased risk of complication for wound healing.

Other inhibitors of angiogenesis. Although anti-VEGF drugs are most commonly used for the treatment of cancers and retinal disease, a number of other FDA-approved inhibitors have anti-angiogenic properties and have been shown or have the possibility to affect wound healing. Anti-EGF receptor (EGFR) drugs (cetuximab and panitumumab) are used for the treatment of advanced renal cell cancer. These drugs have been found to affect wound healing.^{42,43} EGF is a key signaling molecule in stimulating epithelial cell motility and required for re-epithelialization. It is also a major stimulator of fibroblasts, endothelial migration, and wound contraction. There are currently two FDA-approved inhibitors of mammalian targets of rapamycin (mTOR). mTOR is a serine/threonine protein kinase that regulates cell proliferation, motility, and survival, and it is up-regulated under hypoxic conditions and promotes angiogenesis.⁴⁴ In addition, there are a number of FDA-approved topical agents being used by dermatologists that have been shown to possess antiangiogenic properties (alitretinoin, imiquimod, and polyphenon E) which could affect wound healing if a surgical procedure occurs in the area of treatment. With the advent of anti-angiogenic treatments, surgeons have to be acutely aware of patients using these medications due the increased risk of complication or delayed wound repair. Thus, caution should be taken with these patients when performing surgical procedures.

Wound-healing complication due to anti-angiogenic drugs

Angiogenesis plays an important role in the proliferative phase of wound healing, and the disruption of angiogenesis during this phase has been shown to affect the reconstruction of dermal integrity.⁴⁵ In addition, it is well established that the suppression of cell proliferation significantly affects wound integrity; thus, VEGF and FGF play a vital role in the initiation and progression of the granulation phase.

Systemic inhibition of VEGF has been observed to promote a number of complications, which in-

clude wound dehiscence, surgical site bleeding, incisional hernias, erosions, ecchymoses, proteinuria, thromboembolic events epistaxis, hemoptysis, skin rash, hypertension, gastrointestinal perforations, and infections.^{45,46} Common wound-healing complications observed with the administration of anti-VEGF drugs (bevacizumab) is the occurrence of wound dehiscence, ecchymosis, surgical bleeding, and wound infection.⁴⁷ These complications are attributed to the inhibition of endothelial cells' response to injury.

A number of bleeding complications have been observed from continued uses of anti-VEGF drugs. The most common complication has been nosebleeds (epistaxis) with bevacizumab showing an incidence rate of 44% and the anti-tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib being 26% and as much as 60%, respectively, in patients.⁴⁸ This is thought to be a result of the platelet uptake of these drugs. Platelets have a significant store of VEGF in their α -granules, and the uptake of these drugs has been shown to neutralize 97% of VEGF activity within 8 h of administration.⁴⁸ In addition, platelets express VEGFR, which plays a role in platelet activation. Thus, anti-VEGF drugs can reduce platelet activation and induce thrombocytopenia. VEGF also induces endothelial expression of tissue factor, which is a major regulator of the coagulation cascade and may be a factor for the disruption of the wound-healing process.⁴⁸ Since FGF plays a critical role in granular tissue formation, the additional use of anti-FGF inhibitors in conjunction with anti-VEGF inhibitors may further increase the incidence and severity of wound-healing complications.

Anti-angiogenic drug toxicities. The use of anti-angiogenic agents was initially proposed to be a more specific and less toxic approach for the treatment of cancer, due to the quiescent nature of the vasculature in adults. Although many of the anti-angiogenic agents are well tolerated, the long-term use has led to a significant number of adverse reactions. These toxicities are enhanced with the use of the TKIs. These inhibitors target multiple signaling pathways, and toxicity may arise due to concomitant inhibition of several pathways. Some of the common adverse reactions from long-term use are hypertension, hemorrhage, gastrointestinal perforation, arterial thromboembolism, epistaxis, proteinuria, myocardial infarction, subdural hematomas, and skin toxicities.⁴⁸

A number of skin toxicities have been observed with extended use of these inhibitors (Table 3). Hand-foot syndrome (palmoplantar erythrodysesthesia)

Table 3. Cutaneous side effects of anti-VEGF drugs

Bevacizumab	Sunitinib	Sorafenib
Acneiform eruption	Palmoplantar	Palmoplantar
epistaxis	erythrodysesthesia	erythrodysesthesia
Xerosis	Xerosis	Xerosis
Exanthems	Alopecia	Alopecia
Scaling	Exanthems	Exanthems
Erythema	Skin discoloration	Scalp folliculitis
Skin discoloration	Depigmentation	Pruritus
Wound healing	Wound healing	Erythematous facial scaling
Delayed	Dehiscence	Seborrheic dermatitis
Dehiscence	Ecchymosis	Perforating folliculitis
Ecchymosis		
Bleeding		

has been a common observation. It is thought to be manifested by swollen epidermal cells, dilated capillaries, and apoptotic endothelial cells. This toxicity is observed more often with the administration of sunitinib and imatinib than bevacizumab, suggesting that the effects are a result of off-target tyrosine kinase receptor inhibition.⁴⁸ Other complications that have been observed are dehiscence, xerosis, exanthems, scaling, and delayed wound healing. In many cases, these cutaneous side effects are dose dependent and can be reversed by a reduction in dosage or discontinuation for a short period of time.⁴⁹

Administration. Determining the optimal effective drug dosage is typically done by measuring the inhibition of a target pathway. With angiogenesis inhibitors, this is more difficult, as there are no distinct markers for angiogenesis.⁵⁰ Therefore, dosage is typically determined by maximum tolerated dose. This is observed as a percentage of patients who develop specific cutaneous side effects of grade 3 toxicity. For anti-angiogenic antibodies, body weight is used to determine dosage and small molecules are usually determined by plasma concentrations.

The humanized monoclonal antibody inhibitors (Table 1) are administered by intravenous infusion. Bevacizumab is administered at 5–15 mg/kg every 14–21 days depending on the type of cancer being treated and whether chemotherapy is being administered. It has a circulating half life of ~20 days, and the steady state is predicted at 100 days. Cetuximab is administered with an initial dose of 400 mg/m² followed by a 250 mg/m² weekly dose. The small-molecule inhibitors are typically administered orally (Table 1) and have a half life of hours. Sunitinib is administered at 37–50 mg/day depending on the cancer being treated, and sorafenib is administered at 2 × 400 mg/day. Ranibizumab, pegaganib, and bevacizumab are admin-

istered intravitreally for the treatment of retinal diseases. Ranibizumab is recommended at 0.5 mg/month once visual acuity is maintained; then, dosage can be reduced to 4–6 doses/year. For the treatment of retinal diseases, pegaganib is administered at 0.3 mg every 6 weeks and bevacizumab administration is 1.25 mg every 4–6 weeks. The administration of all anti-angiogenic drugs is continuous until the development of side effects, at which time the patient may receive a temporary dose reduction or interruption to reduce the observed side effects.

For the antibody inhibitors, the anti-VEGF inhibitor (bevacizumab) causes less frequent and less severe cutaneous side effects compared with the anti-EGF inhibitor (cetuximab).^{48,49} The most common toxicity (grade 3/4) of bevacizumab is bleeding that occurs in 4% of patients, then wound-healing complications (4%) and proteinuria (3%), which developed between 3 and 9 months of treatment.⁵¹ On the other hand, the TKIs demonstrate a higher incidence of side effects.^{48,49} For these inhibitors, cutaneous side effects are predominantly observed after 3–4 weeks of treatment.⁴⁹ Due to the recent availability of these drugs (bevacizumab was the 1st to receive FDA approval in 2004), there are little long-term (years) data regarding the side effects of these drugs, and more studies are needed to gain a better understanding of the potential risk factors that may occur with long-term use.

Management recommendations for surgery. Although the incidence of grade 3 toxicities is relatively small, <5% for most toxicities, the potential for wound-healing complications is a major concern due to the importance of angiogenesis for wound healing. With the increased usage of anti-angiogenic therapies for the treatment of advanced malignancies and retinal disease, it is important for the proper management of surgical patients being prescribed angiogenic inhibitors to reduce the risk of wound-healing complications. Therefore, caution should be taken when electing to perform surgery on patients being administered anti-angiogenic drugs. Surgeons should take into account the potential hazards of increased wound-healing complications, as the current data support an increase in incidents of wound complications.^{48,49}

The half life of the monoclonal antibody is typically longer, 7.5 days (panitumumab) to 28 days (trastuzumab), than the TKIs, 2.5 h (axitinib) to 50 h (sunitinib). For patients being administered antibody therapy, the duration for discontinuation of treatment before surgery is significantly greater

than that required for TKIs. A general recommendation is to discontinue usage at least 30 days before surgery with some recommendations suggesting as much as 8 weeks in the case of breast cancer.⁵² For postsurgical, a minimum of 4 weeks is recommended before continuation. This is highly dependent on assessment of the wound status and tumor growth. Although a number of studies have been conducted looking at wound healing complications, there are only a few studies for each type of cancer, thus limiting the data that can be extrapolated from these individual studies.⁴⁷

With the half life of the small-molecule TKIs, typically <24 h, 1 week of discontinued use is recommended before surgery.⁵³ Postoperative initiation of treatment is recommended at a minimum of 4 weeks. There are very few comprehensive studies on the effects of TKI on wound-healing complications; therefore, this recommendation is based on the average time (28 days) for dermal wound healing and on the literature from bevacizumab.⁴⁷ The TKIs pazopanib, sorafenib, and sunitinib are most commonly associated with cutaneous side effects. The most common was palmo-plantar erythrodysesthesia and erythema, but prospective studies have not been carried out for their effects on wound healing. Further studies are needed to gain a greater understanding of the effects that TKIs have on wound healing and to provide proper management of patient care.

SUMMARY

The use of angiogenic inhibitors in the treatment of advanced malignancies has been beneficial in the treatment of cancer. This has led to their use in the treatment of neovascular diseases. Although anti-angiogenesis drugs have been shown to be beneficial in the treatment of cancer, they also cause severe skin toxicities and are responsible for wound-healing complications. With the increased use of angiogenic inhibitors to treat a growing number of malignancies, there will be a greater requirement for clinicians and surgeons to manage patient care to reduce potential wound-healing complications. At present, anti-angiogenic drugs

TAKE-HOME MESSAGES

- Angiogenesis is critical for wound repair.
- VEGF and FGF, potent angiogenic factors, play a significant role in wound healing.
- Serious and common toxicities of anti-angiogenic drugs include wound healing complications, such as dehiscence, ecchymosis, and bleeding.
- Cutaneous side effects, in most incidences, can be alleviated with a dose reduction or interruption.
- Toxicity is observed more often with the administration of TKIs than antibody inhibitors.
- For surgical procedures, drug usage should be discontinued (at least 30 days for antibody inhibitors and 7 days for TKIs) before surgery and restarted at a minimum of 4 weeks postsurgery.

are administered individually but with an increasing incidence of tumor resistance to anti-VEGF therapy, combining multiple anti-angiogenic drugs is not being considered. A combination strategy will most likely increase the incidence and severity of wound-healing complications. Thus, successful management of these drugs becomes important for reducing the severity of cutaneous side effects and wound-healing complications. Although there is a significant number of studies that have looked at wound-healing complications, most have a small sample size and are retrospective. These studies in most cases are inadequate to precisely delineate the risk of wound-healing complications or cutaneous side effects. Thus, further studies are necessary to identify the risk of wound-healing complications and to optimize management guidelines to reduce the incidence of poor wound healing and adverse cutaneous events.

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Abbreviations and Acronyms

AKT = protein kinase B
 DAG = diacylglycerol
 ECM = extracellular matrix
 EGF = epidermal growth factor
 EGFR = EGF receptor
 eNOS = endothelial nitric oxide synthase
 ERK = extracellular signal regulated kinase
 Fak = Focal adhesion kinase
 FGF = fibroblast growth factor
 FGFR = FGF receptor
 Flk-1 = vascular endothelial growth factor receptor-2
 Flt-1 = vascular endothelial growth factor receptor-1

GRB2 = growth factor receptor-bound protein 2
 HSP = heat shock protein
 IP-10 = interferon- γ inducible factor-10 kDa
 IP3 = inositol trisphosphate
 MAPK = mitogen activated protein kinase
 MEK = mitogen activated protein kinase kinase
 MEKK = MAPK/ERK kinase kinase
 mTOR = mammalian target of rapamycin
 PDGF = platelet-derived growth factor
 PDGFR = PDGF receptor
 PIGF = placental growth factor
 PIP2 = phosphatidylinositol 4,5-bisphosphate
 PKA = cAMP-dependent protein kinase
 PKC = protein kinase C
 PLC- γ = phospholipase C- γ
 Shc = Src homology 2 domain-containing
 SOS = son of sevenless
 TKIs = tyrosine kinase inhibitors
 VEGFR = VEGF receptor
 VEGF = vascular endothelial growth factor