Angiogenesis and vascular malformations: Antiangiogenic drugs for treatment of gastrointestinal bleeding

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Abstract

Treatment of gastrointestinal bleeding in patients with angiodysplasias and Osler's disease (hereditary hemorrhagic telangiectasia) is clinically challenging. Frequently, vascular malformations occur as multiple disseminated lesions, making local treatment an unfavorable choice or impossible. After local therapy, lesions often recur at other sites of the intestine. However, as there are few therapeutic alternatives, repeated endoscopic coagulations or surgical resections are still performed to prevent recurrent bleeding. Hormonal therapy has been employed for more than 50 years but has recently been shown to be ineffective. Therefore, new therapeutic strategies are required. Understanding of the pathophysiology of angiogenesis and vascular malformations has recently substantially increased. Currently, multiple inhibitors of angiogenesis are under development for treatment of malignant diseases. Experimental and clinical data suggest that antiangiogenic substances, which were originally developed for treatment of malignant diseases, may also represent long-awaited specific drugs for the treatment of vascular malformations. However, antiangiogenics display significantly different actions and side-effects. Although antiangiogenics like thalidomide seem to inhibit gastrointestinal bleeding, other substances like bevacizumab can cause mucosal bleeding. Therefore differential and cautious evaluation of this therapeutic strategy is necessary.

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Key words: Angiodysplasias; Osler's disease; Angiogenesis; Gastrointestinal bleeding; Vascular endothelial growth factor

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INTRODUCTION

Diseases related to vascular malformation and pathologic vessel growth include benign conditions such as pediatric hemangioma, cutaneous angiectasias and venous malformations. They also include more severe and potentially life-threatening diseases like gastrointestinal angiodysplasias, Osler's disease (hereditary hemorrhagic telangiectasia, HHT) and cerebral arteriovenous malformations, as well as rare syndromes like hereditary dysembryoplasia and pulmonary capillary haemangiomatosis. Vascular malformations and dysfunctional vessels in these diseases result from different disturbances of the angiogenic process, which have only been partially characterized^[1-3].

Among these anomalies, arteriovenous vascular malformations that are located on mucosal surfaces are of special clinical relevance because such lesions may cause intense bleeding. Other symptoms of arteriovenous vascular malformation include shunt syndromes, compression syndromes and thrombocytopenia/coagulopathy (Kasabach-Merritt syndrome).

Both Osler's disease and gastrointestinal angiodysplasias can cause recurrent bleeding, which in severe cases can require hundreds of blood transfusions over a period of years^[4,5]. Despite diagnostic improvements like wireless capsule endoscopy, treatment of such patients remains a clinical challenge. Multiple lesions disseminated over the small intestine are frequently present, making local treatment an unfavorable choice or impossible^[4]. However, as there are few therapeutic alternatives, repeated endoscopic coagulation or surgical resection is performed to prevent recurrent bleeding (although lesions often recur at other intestinal sites after local therapy). Therefore an effective medical treatment for these patients is urgently needed.

Although multiple drugs have been evaluated, there is currently no medical treatment with confirmed efficacy for preventing bleeding from vascular malformations. In this situation, hormonal therapy, which is still the best evaluated treatment option, is frequently employed. Based on observations of cycle-dependent severity of bleeding in some patients, hormonal therapy with estrogens and progesterones has been used for prevention of bleeding since the 1950s. However, there have been no confirming data regarding the effectiveness of hormonal therapy for prevention of intestinal bleeding. The only double-blind, placebo-controlled trial for treatment of nasal bleeding in Osler's disease suggested a moderate effect, but found no

significant reduction in epistaxis from estradiol therapy^[6]. In 72 patients with non-hereditary angiodysplasias, a recent randomized placebo-controlled study failed to show an effect from a combination of ethinyl estradiol and norethisterone on the incidence of rebleeding and transfusion requirements^[7]. Due to these disappointing results and substantial side-effects, especially in male patients, new therapeutic approaches are clearly required.

MECHANISMS OF BLEEDING

Understanding of the pathophysiology of angiogenesis and vascular malformation has recently substantially increased. Different mutations within the angiogenic signaling cascade indicate that two types of Osler's disease can be differentiated. Mutations of endoglin or activin receptor-like kinase 1 (ALK-1), both receptors for transforming growth factor beta (TGF β)^[1,2], are present in the majority of cases of HHT. Differential stimulation of ALK-1 and ALK-5 is thought to regulate different phases of angiogenesis, thereby activating the angiogenic process, with subsequent increased production of vascular endothelial growth factor [VEGF, initially termed vascular permeability factor (VPF)]^[8,9]. VEGF, so far the best characterized angiogenic molecule, stimulates proliferation of vascular endothelial cells and increases vascular permeability, and thus is a central mediator of the early phase of angiogenesis^[10]. Recent studies have confirmed that both Osler's disease and nonhereditary intestinal angiodysplasias are characterized by increased production of VEGF^[11,12]. High serum levels of VEGF that also correlate with severity of bleeding are found in patients with Osler's disease^[11].

Intestinal angiodysplasias in patients who have undergone colonic resections because of recurrent bleeding strongly express VEGF along the endothelial lining^[12], indicating a proliferative phase of angiogenesis. Expression of VEGF receptor 1 is also observed in bleeding intestinal angiodysplasias^[12]. As VEGF receptor 1 is specifically up-regulated by hypoxia, this finding may indicate a role for hypoxia in the pathogenesis of angiodysplasias^[13,14]. However, further detailed analyses are necessary to clarify the pathophysiology of gastrointestinal angiodysplasias.

VEGF-mediated effects are presumably also involved in bleeding in inflammatory bowel disease (IBD). The mucosal inflammation in Crohn's disease and ulcerative colitis is characterized by increased production of the proinflammatory cytokines tumor necrosis factor α , interleukin (IL)-1 and IL-6. In experimental models, proinflammatory cytokines have been shown to induce VEGF^[15,16], a mechanism which is also likely present in IBD in order to supply the inflammatory infiltrate and thickened bowel wall with microvessels^[17]. As a result of permanent VEGF stimulation, sprouting vulnerable vessels are located at the inflamed mucosal surface; thus possibly resulting in intermittent bleeding and so contributing to chronic anemia in Crohn's disease^[18,19]. However, a small number of patients with Crohn's disease also suffers from massive recurrent bleeding^[20,21]. As such episodes of severe bleeding are not associated with high disease activity^[20-22], it can be speculated that the severe bleeding in such patients

results from larger superficially located vessels with arteriovenous short circuits. Angiodysplasias have been documented in several of these patients; however they have not been definitely proven to cause this bleeding^[20-22].

The initial phase of angiogenesis is characterized by VEGF-dependent formation and the sprouting of vessels consisting of endothelial cells. Within this process, microenvironmental concentrations of VEGF seem to determine whether normal or aberrant angiogenesis is induced^[23]. Gene-therapy-induced high local concentrations of VEGF result in vascular malformations^[24]. Such lesions resemble the chaotic architecture of haemangiomas or angiodysplasias and are characterized by thin-walled fragile vessels with high permeability, which lack smooth muscle cells and are susceptible to rupture^[25]. To mature, such a primitive vascular plexus would have to be remodeled and vessels acquire a smooth muscle layer, a process that requires other angiogenic factors such as TGF β , platelet-derived growth factor and angiopoietin-1 (which also stabilizes the leakage of VEGF-overexpressing vessels)^[25,26]. Angiodysplasias and other vascular malformations like hemangiomas arise from massive local activation of the early stage of angiogenesis, with accumulation of VEGF, which induces primitive endothelial vessel complexes. However, these vessel precursors fail to finally differentiate into complete functional vessels and form net-like labyrinthine complexes. If surrounded by parenchymal tissue or stable epithelial structures, these complexes are generally harmless. However, when located near a mucosal surface, such fragile vessel systems are susceptible to rupture and can cause bleeding.

ANTIANGIOGENIC THERAPY

The observation that different vascular malformations, despite a distinct pathogenesis, are characterized by a pathologic accumulation of VEGF theoretically makes them an attractive target for direct or indirect VEGF-suppressive antiangiogenic therapy. Suppression of VEGF disrupts development of sprouting vessels: in experimental models VEGF withdrawal results in endothelial cell shedding and regression of primitive hemangioblastoma-like vessels^[27].

Several antiangiogenic substances have been developed for treatment of malignant diseases. These include monoclonal antibodies against VEGF [Bevacizumab (Avastatin)], VEGF-trap, VEGF-receptor antibodies and antagonists [SU5416 (semaxanib), IMC-IC11, PTK 787 and SU6668], proteins (endostatin and angiostatin), matrix metalloproteinase inhibitors (Marimastat, Primostat and COL-3), thalidomide and its analogues [CC5013 (Revimid) and CC4047 (Actimid)], and several other substances that act during different phases of the angiogenic process^[28]. In addition to their therapeutic potential in malignant diseases, some of these substances could also be useful for treatment of bleeding vascular malformations.

THALIDOMIDE-THE FIRST ANTIANGIOGENIC DRUG

The best known-and for four decades unrecognized as

such-inhibitor of angiogenesis is thalidomide, which tragically was used as a sedative and anti-emetic in pregnant women from 1956 until it was withdrawn from the market in 1961 after being recognized to have caused severe birth defects. During these years, in which thalidomide became the most popular sedative in Germany, about 10000 children with phocomelia and other malformations were born^[29]. It was only in 1994 that thalidomide was found to inhibit VEGF-and basic fibroblast growth factor-mediated angiogenesis; a detection that resulted from a side-effect-based literature screening in search of drugs with antiangiogenic activity that D'Amato and Folkman presumed should cause both amenorrhea and fetal malformations^[30]. The exact mechanism by which thalidomide acts within the angiogenic cascade remains to be determined, but appears to be located upstream of the VEGF level, i.e. reduced expression of integrin genes has been hypothesized^[31]. In experimental models, the antiangiogenic activity of various thalidomide metabolites correlates with teratogenicity^[30-32], indicating that antiangiogenic effects are also mainly responsible for thalidomide-related birth defects in humans. The antiangiogenic potential of thalidomide is currently being evaluated for treatment of several malignant diseases^[29]. Due to promising results in patients with therapy-refractory multiple myeloma, thalidomide is now evaluated as both first-line myeloma therapy and in combination with hematopoietic-cell transplantation^[33,34].

It has recently been reported in a number of case studies that thalidomide reduces the incidence of severe bleeding in different gastrointestinal diseases. Eight patients with severe bleeding related to Crohn's disease or angiodysplasias of the small intestine, who had received up to 230 blood transfusions, responded to moderate doses of 100-300 mg thalidomide daily^[18,22,35]. Similarly, chronic bleeding unexpectedly resolved in patients with hereditary hemorrhagic telangiectasia, who received thalidomide as antiangiogenic cancer therapy^[36,37]. In patients with angiodysplasias, rebleeding was also prevented for more than 2 years after thalidomide treatment had ended^[22]. In Crohn's disease with moderate inflammatory activity, severe bleeding stopped during thalidomide treatment, partly recurred after cessation of thalidomide, but was controlled again by retreatment^[18,22]. However, in patients with Crohn's disease, it is not clear whether cessation of bleeding is related to antiangiogenic or anti-inflammatory effects of thalidomide. More objective evidence that antiangiogenic effects of thalidomide are responsible for the efficacy on bleeding is found in patients with non-inflammatory diseases. In patients with angiodysplasias or Osler's disease without any evidence of inflammation^[22,35,37], the efficacy of thalidomide on bleeding is unlikely to be related to anti-inflammatory or immunomodulating effects. Serum levels of VEGF were found to be suppressed by thalidomide in patients without inflammation^[22]. In patients with multiple angiodysplasias of the small bowel, wireless capsule endoscopy has demonstrated that the clinical efficacy of thalidomide is paralleled by a decrease in number, size and color intensity of angiodysplasias, which indicates regression^[38].

Although the results of the above case series need to be confirmed in controlled trials, present data indicate that antiangiogenic effects of thalidomide are responsible for reductions in bleeding episodes. However, the side effects of thalidomide are also substantial. Thalidomide is a potent sedative, causes severe birth defects and can also induce sensible peripheral neuropathy, especially at higher cumulative doses^[39], therefore, it may not turn out to be the drug for treatment of vascular malformations hoped for by clinicians. Furthermore, in addition to its antiangiogenic activity, thalidomide exerts immunomodulating effects^[29]. It is possible that other newly developed antiangiogenics will show more specific inhibition of VEGF or other steps within the angiogenic cascade, with possibly fewer side effects.

NEW ANTIANGIOGENICS

Of the currently developed antiangiogenic substances, most information regarding clinical efficacy and toxicity is available for bevacizumab (Avastatin[®]), a humanized monoclonal antibody against VEGF. Bevacizumab was recently shown to be effective in the treatment of colonic and renal cancer; present data indicate strong antiangiogenic activity and a favorable side-effect profile^[40,41]. However, nose bleeding is frequently observed during treatment (in up to 59% of patients)^[42]. The incidence of nose bleeding correlates with higher doses^[40], although the reason for this bleeding is not clear. A loss of vascular integrity by bevacizumab-induced endothelial-cell shedding in highly regenerative mucosal tissues with active angiogenesis could be a possible explanation for this dose-dependent effect. Other reported side effects during treatment with bevacizumab include gastrointestinal bleeding and perforations, which were not always tumor-related^[41,42].

Bleeding complications do not seem to be a specific feature of bevacizumab. A recent study with IMC-IC11, a humanized monoclonal antibody against VEGF receptor 2, also reported bleeding episodes unrelated to tumor manifestations^[43]. Although most bleeding complications are probably of minor relevance in patients with malignant diseases, it is conceivable that abrupt antibody-induced withdrawal of VEGF in proliferating VEGF-dependent endothelial vessels could become critical in pre-existing vascular malformations located on mucosal surfaces.

Therefore, although VEGF-based antiangiogenic therapy is a promising and highly specific therapeutic option for preventing growth of vascular malformations, it seems questionable whether monoclonal antibodies against VEGF or its receptors are also useful for treatment of bleeding from pre-existing vascular malformations. Indeed, some highly effective antiangiogenics could even aggravate bleeding from vascular malformations.

Semaxanib (SU 5416), a small-molecule inhibitor of VEGF receptor 2 tyrosine kinase has recently been used for treatment of hemangioblastoma in patients with von Hippel-Lindau disease (vHLD). In vHLD, a loss of von Hippel-Lindau protein results in an accumulation of hypoxia-inducible factor and subsequently, induction of

VEGF^[44]. Some initial studies on semaxanib have reported regression or stabilization, with improvement of macular edema, in patients with hemangioblastoma, which indicates effective inhibition of VEGF^[44,45]. Frequently observed side effects of semaxanib include fatigue and headache^[47,48]. To date, bleeding complications, like those found for bevacizumab, have not been reported for semaxanib (neither have they been reported for thalidomide, for which side effects have been well documented since its reevaluation for malignant and inflammatory diseases).

In summary, it remains unclear why some antiangiogenic substances like bevacizumab can cause mucosal bleeding and others like thalidomide do not. This effect may be related to the phase of angiogenesis that is antagonized, or might reflect a particular strong antiangiogenic activity. Detailed analyses of the angiogenic cascade and how thalidomide and other antiangiogenics act within this process will be needed to resolve this issue.

SIDE-EFFECTS AND TOXICITY

Currently, only limited data are available regarding the general toxicity of antiangiogenic therapy. Arterial hypertension has been reported for several agents and is thought to be at least partially related to reduction of VEGF-mediated vascular permeability. As VEGF is also centrally involved in neuroregeneration, neurotoxicity is another possible concern for antiangiogenic treatment^[49]. Experimental peripheral neuropathy is reversible by VEGF gene transfer^[50]. Reduction of VEGF levels by 25% results in motor neuron degeneration reminiscent of amyotrophic lateral sclerosis^[51]. Thalidomide's well-documented neurotoxicity is therefore possibly not drug-specific but could be a general effect of long-term antiangiogenic therapy. Until now, significant neuropathy has not been reported for the new antiangiogenics; however, only very limited data regarding long-term toxicity are available. Furthermore, as these drugs are generally just one part of a polychemotherapeutic regimen, it is often unclear to what extent antiangiogenics contribute to clinically observed neurotoxicity^[52].

Finally, VEGF is also crucial for embryonal angiogenesis and vasculogenesis. Loss of a single VEGF allele causes severe embryonic vascular defects^[53]. Therefore, not only thalidomide, but any inhibitor of VEGF that crosses the placenta has to be considered a potential teratogen. As antiangiogenics are primarily developed as anticancer agents and designated to be used in combination with chemotherapy, this subject is generally regarded as of minor relevance. However, if antiangiogenic therapy is expanded to benign diseases like angiodysplasias, Osler's disease, and inflammatory diseases like Crohn's disease (which may also improve due to inhibition of angiogenesis)^[54-57], and young women are candidates for treatment, teratogenicity becomes a critical issue. Indeed, a single dose of thalidomide is sufficient to cause birth defects^[30]. Angiogenesis has a central role in embryo growth and pregnancy-prevention programs cannot completely prevent the birth of children with fetal malformations^[58]; therefore, antiangiogenics should only be used under strict surveillance in non-malignant diseases.

CONCLUSION

In summary, antiangiogenic substances like thalidomide hold promise to be not only useful for treatment of malignant diseases, but may also represent the drugs that have been long awaited for the treatment of bleeding from vascular malformations. However, as some antiangiogenics can cause mucosal bleeding, a differential therapeutic approach and careful evaluation are necessary. Moreover, antiangiogenic therapy is also teratogenic and therefore has to be very cautiously considered in women of child-bearing potential.

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