Advances in toxicity risk analysis and effective treatments for targeted antiangiogenic drugs

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Abstract: As a hallmark of cancer, angiogenesis is essential for tumor growth and metastasis. In the process of tumor angiogenesis, a number of pathways are involved, which are regulated by stimulators and inhibitors and which are involved in multiple biological processes, including endothelial cell proliferation, migration, cell-cell and cell-matrix adhesion, assembly into tube structures, and apoptosis. Thus, anti-angiogenic therapy targeting tumor blood vessels has received increasing attention, and anti-angiogenic therapy has already became an important component of tumor-targeted therapies. However, the clinical use of anti-angiogenic therapy has not been very successful because of its toxicity, especially when patients suffer from complex conditions or are receiving integrated anti-tumor therapy. In this paper, we retrospectively analyze the toxicity of anti-angiogenic tumor therapy and the corresponding strategies to alleviate or avoid their clinical risk in recent years. The common adverse reactions (hypertension, proteinuria, thrombosis, and dermal toxicity) caused by anti-angiogenesis targeting drugs and their mechanisms are reviewed in detail, and the countermeasures for combating these toxicities are summarized. More reasonable arrangements are given for the corresponding treatment options at different risks. We hope the summary of current theory on the use of clinical anti-angiogenic drugs will shed new light on the discovery and development of anti-angiogenic therapy, as well as tumor rehabilitation.

Keywords: Anti-angiogenesis drugs, toxicity, treatments, target

Introduction

The growth and metastasis of solid tumors are inseparable from the establishment of the tumor vasculature, which supplies oxygen and nutrients to the tumor. Vascular endothelial growth factor (VEGF) is recognized as one of the key factors in tumor angiogenesis [2]. Since one or more of the VEGF ligands or receptors are overexpressed in most solid cancers, using antibodies or small molecule compounds to block the angiogenesis, or anti-angiogenic therapy, is proven to be an efficient way to treat most tumor types [1].

Anti-angiogenic targeted drugs have been used for more than 10 years in anti-tumor therapy [3]. In different types of cancer, it benefits cancer patients by prolonging the survival time, and improving the therapeutic effect. However, the anti-angiogenic effects vary among patients. Compared with traditional anti-tumor chemotherapy drugs, patients have a relatively better tolerance to anti-angiogenic drugs because of their mild side effects [4]. Although the general toxicity of anti-angiogenic targeted drugs is usually tolerated, the potential side effects, as well as the chronic toxicity are associated with a large number of adverse complications and may lead to treatment breaks, or even treatment cessation. Indeed a few individual reactions can even cause life-threatening complications and patient mortality [5]. As a result, health care providers need to closely monitor possible toxic and side-effects and promptly treat mild and moderate adverse reactions. This will not only relieve a patient’s symptoms, but it will also ensure the normal use of the drugs and rationally exert their anti-tumor effects.

VEGF is one of the key mediators in tumor angiogenesis [6-8]. This finding prompted the emergence of a large number of inhibitors
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against VEGF or its downstream signaling pathways [9]. Bevacizumab, a humanized neutralizing antibody targeting VEGF, was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of metastatic colorectal cancer. Since then, several clinical trials have shown that bevacizumab also has a beneficial effect in tumors such as renal cell carcinoma, hepatocellular carcinoma, lung cancer, ovarian cancer, and metastatic melanoma [10-13]. Tyrosine Kinase Inhibitor (TKI), which is an inhibitor targeting the downstream pathway of VEGF, is also represented by a large class of anti-angiogenic drugs, such as sunitinib, sorafenib, vandetanib, and regorafenib. Although anti-angiogenic drugs are widely used in the clinic, cancer patients have not obtained satisfactory results from anti-angiogenic therapy [14].

Currently, anti-angiogenic drugs mainly function as blockers in the anti-VEGF/VEGFR pathway (see Table 1). Compared with traditional chemotherapeutic drugs, anti-angiogenic targeted drugs showed more mild side effects, such as fatigue, gastrointestinal discomfort, and blood myelotoxicity [15]. The occurrence of side effects such as liver and kidney function damage is rare, and the clinical management of these side effects is well established. However, there are still some clinical reports on the occurrence of rare and unique side effects and life-threatening complications. This research mainly summarizes the toxicity and corresponding treatment strategies in the anti-angiogenic treatment of tumors and aims to conclude and further emphasize the risks and treatments of drug use during the treatment of cancer patients. Therefore, it can not only avoid certain risks and ensure the therapeutic effect, but it can also clearly improve patients’ quality of life and prognosis. This review will focus on the occurrence of common adverse reactions of targeted anti-angiogenic drugs.

Common adverse reactions and mechanisms of targeted anti-angiogenic drugs

Hypertension and its mechanisms

Hypertension is one of the most common adverse reactions to anti-angiogenic targeted drugs, and its incidence is between 15% and 60%, depending on the drugs [16]. According to clinical reports, the incidence of the use of bevacizumab and VEGF-TKI drugs is 20% to 30%, and 15%-60%, respectively [17]. Even some studies suggest that all patients with targeted anti-angiogenic drugs will suffer varying degrees of hypertension, but some patients do not show detectable symptoms of hypertension [18]. Hypertension occurs along with the usage of anti-angiogenic targeted drugs, which is closely related to the direct or indirect inhibition of angiogenic factors and their pathways. The VEGF signaling pathway not only promotes the formation and development of tumor blood vessels, but also plays a vital role in maintaining normal vessel wall integrity, endothelial cell growth, and capillary permeability [19]. It is well known that the microvascular system composed of capillaries and small arteries is the main factor for maintaining peripheral blood pressure. As a result, the inhibition of the VEGF signaling pathway will lead to a decrease in blood vessel density by inhibiting the growth and maturation of capillaries, decreasing microcirculation perfusion, and finally affecting blood pressure. VEGF signaling pathway inhibitors can reduce the production of nitric oxide and vasodilatation intermediates by interfering

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**Table 1. The main classification of common anti-tumor angiogenesis targeted drugs**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mechanism</th>
<th>Main target</th>
<th>Representative drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-VEGF antibody</td>
<td>Binding and neutralizing free VEGF</td>
<td>VEGF-A</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>anti-VEGFR antibody</td>
<td>Block VEGF by binding to receptors</td>
<td>VEGFR-2</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>Soluble VEGFR</td>
<td>Binding and neutralizing free VEGF</td>
<td>VEGF-A, PIGF, VEGF-B</td>
<td>Aflibercept</td>
</tr>
<tr>
<td>Small molecule TKIs</td>
<td>Directly acts on VEGFR tyrosine kinase and blocks VEGFR signaling</td>
<td>VEGFR-1, VEGFR-2, PDGFR-β, c-kit, flt-3</td>
<td>Sorafenib, Sunitinib, Regorafenib, Apatinib</td>
</tr>
</tbody>
</table>

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with VEGF function. The combinatorial effect of increased microcirculatory vascular resistance, as well as decreased vasodilatation will eventually lead to the hypertension of patients undergoing anti-angiogenic therapy [20].

Proteinuria and its mechanism

Proteinuria is another common adverse reaction in patients receiving anti-angiogenic therapy. A meta-analysis [21] showed that the incidence of proteinuria is about 21%-63% in all grades of patients using inhibitors against the anti-VEGF signaling pathway. The incidence of proteinuria above Grade 3 is about 2.4%, and the incidence of ADR in patients with renal cancer is even higher. However, the molecular mechanism of drug-related proteinuria in patients is still unclear. A possible explanation is that the VEGF-VEGFR signaling pathway regulates glomerular vascular permeability, and proteinuria may be associated with glomerular filtration barrier damage induced by anti-VEGF and its pathway [21, 22]; In agreement with this hypothesis, the VEGF produced by podocytes plays an important role in maintaining the normal filtration function of capillaries. After VEGF inhibition, endothelial cell swelling, shedding and podocyte dysfunction was observed in the patients, which was characterized by thrombotic microangiopathy, and loss of normal filtration function. Studies have also reported that anti-VEGF-related pathway treatment would cause a loss of proteolytic enzymes in renal tubular epithelial cells, renal tubular dysfunction, and the aggravation of proteinuria [23]. The combinatorial effect of dysfunction and the loss of enzymes in epithelial cells will eventually lead to proteinuria.

Bleeding, thrombosis and its mechanism

The risk of bleeding and thrombosis during the use of anti-angiogenic targeted drugs cannot be ignored. Hemorrhagic reactions induced by anti-VEGF signaling pathways can occur at any stage of treatment, for example, the mild mucosal hemorrhage and tumor-related hemorrhage [24]. CTCI grade epistaxis, silver or vaginal bleeding are the most frequent syndromes of mild skin mucosal hemorrhage in patients. Tumor-related hemorrhage occurs mostly in patients with lung squamous cell carcinoma and metastatic colorectal cancer after bevacizumab treatment. In the event of severe bleeding, the patient may die if not treated promptly. Studies have reported that VEGF-TKI drugs show a higher risk of bleeding at all levels than anti-VEGF monoclonal antibodies [24-26]. For VEGF-TKI drugs, the incidence rate of mild bleeding is about 9%, but the incidence of severe bleeding is basically the same. There are two hypotheses about the mechanisms of anti-VEGF treatment of related hemorrhage [25]: VEGF stimulates endothelial cell proliferation or directly acts on the platelet-induced coagulation process. In addition, anti-VEGF treatment weakens the activity of prothrombin, impairs platelet function and interferes with the blood coagulation process. Because the lesion is adjacent to a large blood vessel or the tumor is deeply infiltrating, the bleeding risk discovery rate itself is higher. In addition, there are many factors that can cause bleeding, such as the use of anticoagulant drugs, anti-rheumatic drugs, radiotherapy, and a vascular-related history of atherosclerosis in patients with the same tumor. Thrombosis includes arterial embolization and venous embolism. Studies have shown that the incidence of arterial embolism is about 3%, and the risk of venous thrombosis is less than 3% [24-26]. A meta-analysis suggests there are no statistical differences between the incidence of anti-VEGF monoclonal antibody and VEGF-TKI drugs [27]. The increased rate in thrombosis is also associated with endothelial cell damage, procoagulant release, and interaction with surrounding cells [28]. On the other hand, anti-VEGF treatment can cause endothelial cell apoptosis and inhibit its regeneration, thereby destroying the integrity of endothelial cells, causing the exposure of subendothelial procoagulant substances and cytokines to accelerate the development of the blood coagulation process. Additionally, anti-VEGF treatment can also cause a decrease in the levels of nitric oxide and prostacyclin, which promote platelet aggregation; moreover, anti-VEGF treatment will increase the erythropoietin content. The increased number of red blood cells leads to increased blood viscosity, which increases the risk of thrombosis.

Dermal toxicity and its mechanisms

During the use of multi-target TKI drugs (sorafenib, sunitinib, apatinib) in anti-VEGF treatment, patients often suffer hand-foot syndrome, rash, alopecia, pigmentation, or skin
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**Table 2.** Classification and treatment of hypertension caused by anti-tumor angiogenesis targeted drugs

<table>
<thead>
<tr>
<th>NCI-CTC Level</th>
<th>Clinical manifestation</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Prehypertension</td>
<td>No intervention required</td>
</tr>
<tr>
<td>Level 2</td>
<td>Repeated or persistent symptomatic systolic blood pressure increased</td>
<td>Treatment with antihypertensive drugs</td>
</tr>
<tr>
<td>Level 3</td>
<td>Systolic blood pressure ≥160/100 mmHg</td>
<td>Need better antihypertensive drug or higher intensity treatment; suspend or reduce the amount of targeted drugs</td>
</tr>
<tr>
<td>Level 4</td>
<td>Life-threatening (such as hypertensive crisis)</td>
<td>Actively treat high blood pressure and permanently stop anti-angiogenic drugs</td>
</tr>
</tbody>
</table>

discoloration [29]. Bevacizumab will cause back rash according to some reports, but it often occurs during the infusion process and may be relevant to the infusion reaction [30]. TKI drug-induced skin reactions are commonly seen in the following conditions: ① hand-foot syndrome; ② facial red spot rash; ③ rash and itching; ④ alopecia and skin pigmentation and discoloration. The mechanisms of the first three cases are still unclear, but alopecia and skin changes may affect the activity of signal molecules in the hair follicle melanocytes or c-kit pathways by VEGF-TKI drugs, thereby inducing the formation of these changes [29, 30].

**Toxic treatments of targeted anti-angiogenic drugs**

**Treatments of hypertension**

Hypertension is one of the most common ADR in patients, and the treatments are largely symptomatic [31]. Patients should take measures to monitor their blood pressure at least 3 times a day, master the basics of blood pressure, and then determine what type of hypertension they have. 60% of patients with hypertension are salt-sensitive, so for them it is necessary to limit the intake of salt in a balanced diet. According to the classification of hypertension, doctors need to consider whether to use a drug therapy [31, 32]. Hypertension classifications and treatments are shown in Table 2: it is worth noting that the recommended antihypertensive drugs in patients include angiotensin-converting enzyme inhibitors (ACEI), Angiotensin II receptor antagonists (ARB), diuretics, and β blockers. Typically, diuretics are not recommended in patients with renal dysfunction, or patients with proteinuria. If necessary, consult a specialist for antihypertensive medication [32]. Finally, drug-related hypertension is usually caused by microcirculation, and sometimes some patients have kidney disease, so it is necessary to monitor the renal function of urine protein in patients with anti-vascular targeted therapy. If there is an intolerable clinical symptom of hypertension, the usage of targeted drugs must be stopped.

**Treatment of proteinuria**

Under normal circumstances, the protein content in urine is 40~80 mg. When the protein content in urine is less than 150 mg, the protein qualitative test is negative [33]. For patients undergoing anti-tumor angiogenesis therapy, the occurrence of proteinuria should be carefully monitored, and a prompt treatment is necessary when proteinuria occurs [34]. First, monitor the change of urinary protein and any changes in the urine routine as a simple and easy method of screening urine protein in patients. If the urine protein is negative, no quantitative test is needed, but if the urine protein test is 2+ or above, it is recommended to perform a 24-hour urine protein quantification and specific classification. The urine protein test can be performed once every 2 weeks. If no abnormality is found, the urine protein test can be taken once every 4 weeks after 2 months. Also, avoid using drugs that will increase the burden on the kidneys, such as Chinese herbal medicines and chemotherapy drugs. If the treatment is temporary, it must be carried out under the guidance of a professional physician. Then, according to the classification of adverse drug reactions, the proteinuria can be divided into 3 levels, according to the level of urine protein, and patients can take different treatment strategies (as shown in Table 3). Lastly, if patients have severe or fatal kidney function damage, the treatment must be suspended. At the same time, for patients with previous renal insufficiency, including renal func-
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Table 3. Anti-tumor angiogenesis targeting drugs that lead to the classification and treatment of proteinuria

<table>
<thead>
<tr>
<th>Levels</th>
<th>Definition</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Proteinuria (+) or 24-hour urine protein quantitation &lt; 1.0 g</td>
<td>Continue treatment at the same dose, closely monitored according to clinical symptoms</td>
</tr>
<tr>
<td>Level 2</td>
<td>Proteinuria (++) or 24-hour urine protein quantitation 1.3-4.0 g</td>
<td>24-hour urine protein quantitation &gt; 2 g, interrupted/down-regulated the dose used; 24-hour urine protein quantitation &lt; 2 g, back to the dose used</td>
</tr>
<tr>
<td>Level 3</td>
<td>24-hour urine protein quantitation &gt; 3.5 g</td>
<td>Repeated appearance of Level 3 proteinuria, need to terminate treatment and suspend medication</td>
</tr>
</tbody>
</table>

Treatment of bleeding and thrombosis

The commonly used strategy of treatment for bleeding and thrombosis is personalized anti-angiogenic targeted therapy, which means the selection of an anti-angiogenic drug is based on the tolerance and efficacy of different patients. The recommended treatments for bleeding are as follows [35]: For patients diagnosed with lung squamous cell carcinoma or patients with a history of bleeding (a single bleeding volume of more than half a teaspoon), using anti-angiogenic targeted therapy is not recommended. If a small amount of bleeding can be controlled in a short period of time, continuing to use these drugs is possible, but the dosage should be adjusted. If local bleeding occurs, surgery, tamponade, radiotherapy, intervention, and other methods can be used to stop the bleeding. For patients with central nervous system metastasis, targeted preconditioning (surgery or radiotherapy) is required to reduce the risk of intracranial hemorrhage before receiving bevacizumab. Moreover, patients with congenital or acquired coagulopathy should use drugs with caution; Last but not least, blood coagulation should be monitored regularly during drug therapy. For the risk of arterial thrombosis, bevacizumab should be used with caution in patients with arterial thrombosis and age > 65 years. Studies have shown that it is safe to use low-dose aspirin and adequate warfarin to prevent arterial thrombosis while receiving bevacizumab treatment [35, 36].

Treatment of dermal toxicity

For patients receiving anti-VEGF treatment or using inhibitors against its related pathways, the occurrence of skin reactions is very common, especially with VEGF-TKI drugs [37]. Mostly, it is a 1-2 grade ADR and does not require special medical treatment. Preventive care, such as avoiding skin irritation and friction, inappropriate shoes or gloves, excessive exercise, standing and manual labor, will effectively alleviate the syndrome [38]. At the same time, keeping skin clean and avoiding secondary infections is necessary. Trying to use moisturizing skin care products is also recommended. When the patient has a grade 3 or above reaction, the treatment should be suspended immediately. For patients with hand-foot syndrome, topical urea steroid can be used for external treatment. When combined with infection, antifungal and antibiotic drugs can be used. When the reaction is reduced to 1-2 grades, the medication can be resumed, and if necessary, the dose can be reduced. When a grade 3 or higher reaction occurs repeatedly, the drug suspension can be considered. Some studies have also reported that the use of COX2 inhibitors or vitamin B6 may reduce the appearance of skin reactions [37-39].

Mathematical research and development of tumor-induced angiogenesis

Establishing mathematical models of tumor-induced angiogenesis is very important for the treatment of tumors [40]. For the past few years, several mathematical models of tumor-induced angiogenesis and hemodynamics have been founded to improve the comprehension of vascular structure and microcirculation dynamics in solid tumors [41-46]. Mc Dougall et al. [43] simulated blood flow and showed that drugs are delivered to the tumor surface through a vascular network from a nearby maternal blood vessel through a related capillary bed, as shown by a mathematical model.
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of its tumor-induced angiogenesis. This is based on the work of Mcdougall et al. and Stephanou et al. [44], who studied the efficiency of drug delivery in 2D and 3D tumor-induced vasculature and assessed the effects of key parameters on tumor uptake and examined how certain capillary removal affects the distribution of blood flow in the system. In addition, Stephanou et al. [45] modeled an adaptive vascular system associated with tumor-induced angiogenesis and deliberated how this adaptive remodeling influences the supply of oxygen and drugs to tumor cells.

Nevertheless, all these models focused on the external capillary network of tumors emerging from the mother blood vessels. Zheng et al. [46] first established a realistic angiogenesis model inside the tumor. A continuous model of tumor growth was used to simulate tumor necrosis, neovascularization, and tissue invasion using the adaptive finite element method, but they did not study blood flow through the network. However, coupling models between blood flow in the tumor microvascular network and interstitial fluid flow in tumor tissue have not been studied more in depth so far. Therefore, this may point to the future direction of the mathematical modeling of tumors.

Discussion

From the 1975 hypothesis to the first anti-angiogenic drug on the market in 2004 (Avastin, Genentech) [47], the inhibition of angiogenesis has come a long way as an anti-cancer treatment. The main obstacle to understanding blood transport in tumors is the heterogeneous architecture of the tumor microvasculature. It is well known that tumors contain many tortuous vessels, shunts, vascular loops, widely variable intervascular distances, and large avascular areas [48]. In addition, tumor vessels are more leaky than normal vessels, which may improve the fluid exchange efficiency between the microvasculature and the interstitial space. The microvascular network provides blood and nutrients for the continued development of tumors and provides the initial pathway for invading cancer cells to escape from primary tumors and form metastases. In addition, chemotherapeutic drugs will be transmitted through the capillary network and interstitial space with anisotropic conductivity to the tumor [49]. All of these processes are critically dependent on blood flow within the microvascular network and interstitial fluid flow in solid tumors, which have a major role in solid tumor growth, metastasis, and treatment.

Certainly, as the advances in functional genomics technology continue to accelerate, it is expected that the functions of many more genes in the human genome will be elucidated at an increasing rate [50]. As more and more genes are found to play a direct or indirect role in angiogenesis, new and more suitable anti-angiogenic targets are emerging. For example, angiogenic growth factor Placenta Growth Factor (PLGF) was found to be a homolog of VEGF that forms a heterodimer with VEGF and binds to VEGFR1, which only affects pathological angiogenesis but has no effect on normal physiological angiogenesis. Therefore, PLGF is predicted to be a safe and effective anti-angiogenic drug target compared to VEGF [51]. In addition, advances in pharmaceutical formulations and novel delivery methods will complete the development of novel anti-angiogenic targeted drugs and help advance them into clinical applications.

Anti-angiogenic targeted drugs are increasingly involved in the treatment of colorectal cancer, liver cancer, gastric cancer, lung cancer, kidney cancer, and other malignant tumors, and their therapeutic effects are obvious to all [52]. In order to maximize the therapeutic effect and minimize the toxic and side effects, patients' medical history and basic conditions should be carefully evaluated. A close monitoring of possible toxic and side effects and a personalized treatment is necessary to alleviate the syndrome. It is believed that more cancer patients will be able to use targeted drugs regularly and benefit the greatest from anti-angiogenic targeted therapy.

In conclusion, patients with complex conditions should use single or integrated methods for diagnosis and treatment based on specific conditions. Although many difficulties still exist for the widespread development of antiangiogenic drugs, it is clear that the future of antiangiogenic drugs is promising.

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Disclosure of conflict of interest

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