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REVIEW

Anticoagulation in combination with antiangiogenesis and chemotherapy for cancer patients: evidence and hypothesis

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Abstract: Hypercoagulable state and disorganized angiogenesis are two conspicuous characteristics during tumor progression. There are a considerable number of clinical trials focusing on the effects of anticoagulant and antiangiogenic drugs on the survival of cancer patients. Favorable outcomes have been observed. Excessive blood coagulation not only causes cancer-associated thrombosis, which is a common complication and is the second leading cause of death in patients, but also decreases intratumoral perfusion rates and drug delivery by reducing the effective cross-sectional area of blood vessels. Meanwhile, structural and functional abnormalities of the tumor microvasculature also compromise convective drug transport and create a hypoxic and acidic microenvironment. Vascular normalization strategy can temporarily recover the abnormal state of tumor vasculature by improving blood density, dilation, and leakiness, resulting in enhanced penetration of chemotherapies and oxygen within a short time window. In this article, we first review the evidence to support the opinion that anticoagulant and antiangiogenic therapy can improve cancer survival through several underlying mechanisms. Next, we speculate on the feasibility and value of the combined strategy and discuss whether such a combination has a synergistic antineoplastic effect in cancer patients by way of increasing blood vessel perfusion and drug distribution.

Keywords: tumor microenvironment, anticoagulation, antiangiogenesis, vascular normalization, tumor perfusion

Introduction

Since the French physician Armand Trousseau first described the occurrence of thromboembolic disease in cancer patients nearly 150 years ago, the close relationship between malignancy and excessive blood coagulation has slowly become well recognized. The hypercoagulable state is a universal phenomenon in malignant tumors, which not only seriously impacts local tumor microenvironment but also leads to systemic venous and arterial thrombosis.[1,2] Beyond biological factors, clinical factors, such as bed rest, chemoradiotherapy, central venous catheters, infection, and surgery, are all contributory causes that will determine whether an asymptomatic phenotype manifests clinically.[3] In fact, >90% of cancer patients commonly present with various signs and symptoms of the prothrombotic state that range from one or more asymptomatic coagulation indicators, to clinically defined thromboembolism and disseminated intravascular coagulation.[4] A growing body of studies have proposed that thrombosis is a common complication of malignancy that provokes disease progression and poor prognosis, interferes with patients' quality and expectancy of life, and increases health care costs considerably.[5,6] Hence, anticoagulant therapy

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plays an important role in tumor treatment, even in patients with advanced disease.

During tumor progression, aberrant angiogenesis is another significant feature. Formation of a new vascular network or development of a preexisting vascular bed is initiated by the well-known angiogenesis inducer vascular endothelial growth factor (VEGF). The binding of VEGF to VEGF receptor (VEGFR) stimulates autophosphorylation in certain tyrosine residues. The signal activates downstream pathways and regulates endothelial cell survival and proliferation.[7] Thus, targeting the VEGF–VEGFR pathway has become a considerable therapeutic strategy for cancer treatment. Presently, three primary pharmacological strategies targeting angiogenesis have been created in cancer therapy: 1) the monoclonal antibodies (moAbs) binding VEGF directly such as the anti-VEGF antibody bevacizumab; 2) targeting angiogenesis receptors either with moAbs such as the anti-VEGFR2 antibody or with the inhibitors of tyrosine kinase receptors such as sunitinib and sorafenib; and 3) inhibiting VEGF signaling by recombinant receptor–antibody fusion proteins such as aflibercept.[8] Nevertheless, the fundamentals of these antiangiogenic drugs has not been determined conclusively to this day.

We first summarize the recent studies of tumor microenvironment, including both hypercoagulability and abnormal angiogenesis, in cancer. Next, we elaborate on current clinical evidence and several underlying mechanisms of anticoagulant and antiangiogenic therapy during tumor progression. Finally, we hypothesize whether both the important treatment strategies have a synergistic antineoplastic effect in clinical application that improves the prognosis of the patients, especially by increasing blood vessel perfusion and drug distribution. Furthermore, we give future perspectives in the field of coagulation and angiogenesis in cancer.

Anticoagulant therapy

The association between anticoagulant therapy and tumor disease progression is controversial. Data from different randomized clinical trials suggest a conflicting outcome of low-molecular weight heparin (LMWH) on survival in patients with several types of cancer (Table 1). Therapeutic effects of LMWH display a moderate impact on certain types of cancers, such as small-cell lung cancer.[9–11] It possibly implies that small-cell lung cancer is more sensitive than other cancer types for LMWH treatment. In addition, researchers also notice that LMWH appears to be more effective in patient populations with limited-stage disease, or with a longer estimated life expectancy.[10–12] This may explain the poor results that frustrated researchers on clinical trials that recruited more patients with metastatic or locally advanced cancer. These participants might not theoretically benefit from any antineoplastic effects of LMWH. Despite the fact that the benefit of LMWH therapy on cancer patients' survival is still inconclusive, it is surely associated with a clinically significant reduction in venous thromboembolic event (VTE). Accordingly, with enough consideration in terms of cancer type and stage, anticoagulant therapy, especially LMWH, is a remarkable adjunctive therapy for cancer patients. It is worth noting that these beneficial influences are not completely explained by the prevention and treatment of thrombosis. Several possible interrelated pathology mechanisms have been raised by researchers, including both coagulation-dependent and coagulation-independent activities.

Prevention and treatment of cancer-associated thrombosis

Cancer-associated thrombosis is a prevalent complication in tumor progression and is associated with a poor prognosis.[13] It is estimated consistently that cancer is related to 20%–30% of all first VTE.[14] Due in part to increasing cancer prevalence, improved oncology outcomes, and the use of more effective but prothrombotic therapy regimens (ie, chemotherapy, radiotherapy, hormone therapy, angiogenesis inhibitors, and surgery), a steady increase in the incidence of cancer-associated thrombosis has been observed, during the past 2 decades.[15] Although both venous and arterial thrombosis can be established in cancer patients, the venous thrombotic occlusions have been studied more extensively, including deep venous thrombosis and pulmonary embolism. A retrospective cohort study of over a million inpatients with cancer found an overall prevalence VTE rate of 4.1%, with prevalence incidence enhanced by 28% from 1995 to 2003.[16] A recent systematic review on the absolute risk of VTE in cancer patients found an overall VTE incidence rate of 43 per 1,000 person-years, with a fourfold increased risk compared with the patients with no malignancy.[17] VTE can occur in throughout the cancer process, especially in the first few months after the diagnosis of cancer.[18] Furthermore, thrombotic events are the second most common cause of death in patients with cancer, ranking after death from the cancer itself. Thrombotic event explains 9% of cancer-related deaths, at a high cost to patients and society.[19,20] Accordingly, given the high incidence and mortality, prevention and management of thrombotic events in cancer patients are extremely urgent. Many guidelines

Table 1 Overview of randomized clinical trials of LMWHs on survival of cancer patients

References	Cancer type	Heparin (number of patients)	Regimen	Effect on survival
Kakkar et al[10]	Advanced cancer (breast, colorectal, ovarian, and pancreatic)	Dalteparin (385)	5,000 IU/d, 1 year	Significant increase in median survival in patients with better prognosis (43.5 months vs 24.3 months; *P*=0.03)
Altinbas et al[9]	Small-cell lung cancer	Dalteparin (84)	5,000 IU/d, 18 weeks	Significant increase in median survival (13 months vs 8 months; *P*=0.01)
Klerk et al[69]	Metastasized and advanced cancer (breast, lung, GIT, pancreas, renal, ovary, uterus)	Nadroparin (302)	Therapeutic dose 2 weeks + half dose 4 weeks	Significant increase in median survival in patients with better prognosis (15.4 months vs 9.4 months; *P*=0.01)
van Doormaal et al[70]	Non-small-cell lung cancer, prostate, pancreatic	Nadroparin (503)	Therapeutic dose 2 weeks + half dose 4 weeks	Median survival 11.9 months (placebo) versus 13.1 months (LMWH)
Agnelli et al[71]	Colorectal and lung	Semuloparin (3,212)	20 mg/d, 3.5 months	1-year survival rate 55.5% (placebo) versus 56.6% (LMWH)
Lecumberri et al[11]	Limited small-cell lung cancer	Bemiparin (38)	3,500 IU/d, 26 weeks	Median progression-free survival 272 days (placebo) versus 410 days (LMWH), *P*=0.022 Median overall survival was 345 days (placebo) versus 1,133 days (LMWH), *P*=0.017
Lebeau et al[12]	Small-cell lung cancer	Unfractionated heparin (277)	500 U/kg/d, 5 weeks	Significant increase in median survival (317 days vs 261 days; *P*=0.01); response rates (23% vs 37%; *P*=0.004) At subgroup analysis, the results on survival were obtained for limited diseases (*P*=0.03) but not for extensive diseases (*P*=0.31)

Abbreviations: LMWH, low molecular weight heparin; GIT, gastrointestinal tract.

have been published from international scientific societies. The American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines suggested that prophylaxis with anticoagulant drug is recommended for inpatients with cancer in the absence of bleeding or other contraindications to anticoagulant. By contrast, the European Society of Medical Oncology and American College of Chest Physicians requires bedridden hospital cancer patients with an acute medical complication to be considered for medical thromboprophylaxis in the form of low-dose unfractionated heparin or LMWH. Numerous guidelines acknowledge the significant incidence of VTE in cancer patients undergoing surgery, and recommend surgical patients receive perioperative VTE prophylaxis, although the specific anticoagulant scenarios differ slightly among them.[21–24] Based on the results of several randomized controlled trials and meta-analyses, the use of LMWH is preferred over other anticoagulants in most cases in cancer patients treated for VTE.[25] LMWH is characterized by: lower time for coagulation monitoring, fewer major bleeding events, and once-daily dosing, which make these drugs more appropriate for cancer therapy.[26,27] Fondaparinux is also an acceptable agent for use in initial treatment.[28] Furthermore, aspirin has been shown to hinder arterial thrombosis and to reduce the rate of major vascular events, but there are less data supporting the benefits of therapeutic antiplatelet agents at preventing VTE in cancer patients as well.[29,30]

Anticancer effects

The pathogenesis of the coagulation system imbalance in cancer is likely to be multifactorial, including both coagulation-dependent and -independent activities. A change in the coagulation system itself may conduce the hypercoagulable state. Tumor-specific prothrombotic mechanisms also play a significant role in the complex process. Malignant cells can influence the expression and release of procoagulant factors (ie, tissue factor and cancer procoagulant), inflammatory cytokines, and circulating microparticles, and then activate host coagulation system. The direct stimulation of blood cells, including endothelial cells, platelets, and monocytes, also causes confusion of the hemostatic system;[31,32] vice versa, the disorder of coagulation is closely linked to tumor progression and metastasis as well. Thrombin enlarges cancer cell binding to platelets and

upgrades the metastasizing ability of cancer cells efficaciously in experimental pulmonary metastasis models.[33] In addition, lowering endogenous activated protein C levels will contribute to enhanced metastasis in hypercoagulable mice.[34] Since the first exploration of a potential beneficial antineoplastic effects of anticoagulant drugs was found in 1930, studies have actively investigated how the anticoagulant drugs affect tumor growth and metastasis through multiple mechanisms.[35] Many findings demonstrated that anticoagulants, in particular the LMWH, can affect the growth of primary tumors, block tumor cell heparanase, suppress selectin-mediated tumor cell invasion and metastasis, and inhibit tumor-induced angiogenesis in both in vivo and in vitro systems.[36–39] In addition, the use of aspirin as a cancer chemopreventive agent has a long history of clinical use. Although the antineoplastic effects of aspirin have not been well explained, emerging clinic evidence has shown that constant use of aspirin effectively improves cancer patients' prognosis, particularly those with colorectal cancer.[40] A randomized trial of 311 patients with colorectal adenomas and adenocarcinomas excised by endoscopy showed that the subjects treated with aspirin exhibited lower colorectal tumorigenesis and primary end points with an adjusted odds ratio of 0.60 compared with the subjects in the placebo group.[41] Warfarin, a kind of coumarin anticoagulant, has been known to reduce tumor metastases in mouse and rat models. But the potential mechanisms were mostly ambiguous. Recently, the study by Paolino et al[42] supported a coagulation-independent role of warfarin in tumor metastasis that relies on its inhibitory effect on the Cbl-b/TAM receptors in natural killer cells. It once again raised a major concern regarding the antimetastatic activity of warfarin in cancer treatment. Altogether, these preclinical studies and clinical data further contribute to supporting the proof of potential antineoplastic effects of anticoagulants. It is highly desirable that anticoagulants serve as an adjuvant therapy for cancer treatment in the future.

Increasing blood vessel perfusion and drug penetration

The influence of hypercoagulable state that hamper vessel perfusion is constantly overlooked. It could hamper blood flow in a multitude of ways. On one hand, fibrin and other plasma proteins deposited within the tumor vasculature produce a physiological barrier that reduces the effective cross-sectional area of tumor blood vessels. While on the other hand, tumors are inevitably concomitant with blood capillary ruptures and hemorrhage, resulting in blood leaking into the extracellular matrix, which becomes extravascular thrombosis. Extravascular thrombosis is a mechanical force that generates vessel compression and thus inhibits convective blood flow.[36,43] Therefore, we assume that anticoagulant drugs improve tumor aberrant blood flow in favor of raising the effective concentration of chemotherapeutics in tumor tissue and forming closer contacts between chemotherapeutic agents and tumor cells, which ensures a better therapeutic efficacy. Phillips et al[44] conducted biodistribution studies to determine the effect of LMWH on uptake of paclitaxel (PACL) and doxorubicin (Dox) by breast tumor xenografts. In the MDA453/LCC6 breast tumor xenograft model, they confirmed that LMWH conducts greater [^{124}-I]-PACL intratumoral concentration than that of [^{124}-I]-PACL alone. Similarly, LMWH significantly increased the uptake of Dox in MCF7 Dox-resistant tumor xenografts by 1.5- to 2-fold. Importantly, although LMWH compounds selectively increased tumor uptake of Dox, the drug accumulation in heart and lung tissues, both sites of serious toxicity with this drug, were not increased but reduced. This study credibly demonstrated that LMWH administration considerably improves the efficient distribution of chemotherapeutics and overcomes tumor chemoresistance. The secondary application of anticoagulant drugs might also decrease the doses of chemotherapy required due to more efficient delivery into intratumoral region.[44] The possible mechanisms that explain the improvement of tumor uptake of chemotherapy agents may be complex. As stated earlier, LMWH reduces the deposition of fibrin and other plasma proteins in the blood vessel wall and the extravascular thrombosis, which reopens restricted vessels in the tumor microenvironment. Thus, LMWH and other anticoagulants may overcome the physical barrier and relieve the viscid blood flow by decreasing clotted sediments. This potential effect of anticoagulants is worth exploring thoroughly in further studies, and more direct evidence would likely increasingly support the paradigm.

Antiangiogenic therapy

Angiogenesis, a conspicuous hallmark of malignancy, promotes tumor growth and metastasis by transferring oxygen and nutrients into the tumor mass.[45] In contrast to the healthy vasculature that was arranged in a coherent style, tumor vessels are aberrant in almost all aspects of their structure and function at macroscopic and microscopic levels. The dysfunctional vessels are commonly organized in a more dilated and tortuous shape, and the hyperpermeable vessels with large gaps between endothelial cells, isolated pericytes, and discontinuous or absent basement membranes.[46] A large

quantity of blood plasma leaks into the tumor interstitial space due to the leaky vascular wall, which enhances local interstitial fluid pressure, red blood corpuscle concentration, and blood viscosity.[47] This greatly decreases the blood velocity in focal vascular sections and diverts blood flow to other sites. The abnormal vasculature leads to a hostile tumor microenvironment. It not only reduces tumor blood perfusion but also converts the tumor into an unfavorable hypoxic and acidic microenvironment that diminishes tumor responsiveness to treatments. These pathophysiological characteristics compromise convective transport of drug and impede the effectiveness of conventional anticancer treatments as well as the function of immune cells in tumors.[48–50]

In 1971, Judah Folkman first articulated that antiangiogenic therapy is a promising strategy for cancer and initiated the isolation of tumor angiogenesis factors.[51] The discovery of VEGF as a major regulator of endothelial cell growth and survival paved the way for translating the idea into clinical practice.[52] In 2004, bevacizumab, a humanized moAb directed against VEGF, was approved by the US Food and Drug Administration as first-line treatment for metastatic colorectal cancer, in combination with conventional chemotherapy.[53] The validation of the first antiangiogenic drug opened a new chapter in the development of targeted therapy. Numerous antiangiogenic drugs have been gradually applied to several tumor types over the past 11 years, in particular targeting the VEGF–VEGFR signaling axis.[54] The introduction of these innovative drugs for oncotherapy has resulted in moderate improvements in tumor response and progression-free survival, or overall survival of cancer patients (Table 2). Undoubtedly, the benefits in these randomized trials are not universal, most probably due to heterogeneity of tumor type and therapeutic regimen. Also, antiangiogenic agents are typically given to unselected patients for the approved indications. It is highly desirable to identify reliable predictive markers to select homogeneous groups for more clinical trials.

Although the improved effect has been shown in various tumor types, the principal mechanism of VEGF-targeted drugs has not been explained well to this day. It is credible that different mechanisms have a more or less significant role depending tumor type. Clinical studies have demonstrated that distinct tumor types showed inconsistent responses to different types of VEGF inhibitors or combination regimens. VEGF inhibitors are active as single agents in renal cell carcinoma, hepatocellular carcinoma, and ovarian and neuroendocrine tumors.[55] In these tumors, the original theory of VEGF-targeted drugs may become predominant. The classic concept was that VEGF-targeted therapy can block tumors' blood supply, then reduce the delivery of oxygen and fundamental nutrients, and finally arrest the previously uninhibited tumor cell growth.[56] In contrast, for other tumors such as colorectal cancer (CRC), non-small-cell lung cancer, and breast cancer (although this efficacy is currently pending),[55] VEGF inhibitors are effective only when combined with cytotoxic chemotherapy, seemingly contradicting the initial principal mechanism claims. According to the classical scenario, such suppressive angiogenesis generates spatial and temporal inadequacies of blood perfusion and restrains the intratumoral delivery of coadministered drugs. Moreover, enhanced hypoxia conditions caused by the antivascular effects also render tumor cells relatively chemoradiotherapy resistant and even become more aggressive.[57] Accordingly, given the complexity of tumor biology, such as the heterogeneity of blood vessel growth in different stages and locations, it would be unwise to attribute a single mechanism to VEGF inhibitors in multiple tumor types. In 2001, it has been proposed first that treatment with judicious antiangiogenic agents can transiently revert the abnormal tumor vasculature toward a relatively normal status. Antiangiogenic drugs selectively prune immature blood vessels and retain relatively mature vasculature.[58] The favorable phenomenon, vascular normalization, remodels tumor vessels that show improved connections between adjacent endothelial cells, enhanced pericyte coverage, and tighter association between them.[59] These physiological changes would reduce vascular permeability and result in a drop of intratumoral interstitial fluid pressure.[60] The increase of tumor blood perfusion improves oxygenation and drug delivery and thus inevitably makes tumors more sensitive to chemoradiotherapy.[61] Recently, with positron emission tomography imaging, Chatterjee et al[62] demonstrated that transient antiangiogenic treatment using potent VEGFR/platelet-derived growth factor receptor inhibitor PTK787 produces a transient time window of improved tumor blood flow with reduced leakiness and improved pericyte coverage. This short-lived normalization window results in improved outcomes of erlotinib administration.[62] Similarly, Batchelor et al[63] applied magnetic resonance imaging techniques and blood biomarkers in prospective Phase II clinical trials to show that the addition of cediranib, a pan-VEGFR tyrosine kinase inhibitor, to chemoradiation improved vascular integrity and blood perfusion in 20 of 40 (50%) newly diagnosed glioblastoma patients, compared with only one of 14 (7%) patients treated with conventional chemoradiation alone, and was associated with improved tumor oxygenation status. Of note, these newly diagnosed glioblastoma patients with improved tumor blood perfusion and oxygenation status after

Table 2 Chemotherapy in combination with antiangiogenic agents in randomized trials in various malignancies

References	Tumor type	Regimen (number of patients)	PFS (months)	OS (months)
Saltz et al[72]	CRC	FOLFOX-4/XELOX + bevacizumab (701) FOLFOX-4/XELOX + placebo (699)	9.4 versus 8.0 (HR =0.83; *P*=0.0023)	21.3 versus 19.9 (HR =0.89; *P*=0.0769)
Giantonio et al[73]		FOLFOX-4 + bevacizumab (290) FOLFOX-4 + placebo (289)	7.3 versus 4.7 (HR =0.61; *P*<0.0001)	12.9 versus 10.8 (HR =0.75; *P*=0.0011)
Van Cutsem et al[74]		FOLFIRI + aflibercept (612) FOLFIRI + placebo (614)	6.9 versus 4.67 (HR =0.758; *P*=0.00007)	13.5 versus 12.06 (HR =0.817; *P*=0.0032)
Tabernero et al[75]		FOLFIRI + ramucirumab (536) FOLFIRI + placebo (536)	5.7 versus 4.5 (HR =0.793; *P*<0.0005)	13.3 versus 11.7 (HR =0.884; *P*=0.0219)
Sandler et al[76]	NSCLC	CbP + bevacizumab (434) CbP (444)	6.2 versus 4.5 (HR =0.66; *P*<0.001)	12.3 versus 10.3 (HR =0.79; *P*=0.003)
Reck et al[77]		CG + bevacizumab (345) CG + bevacizumab (351) CG + placebo (347)	6.7 versus 6.5 versus 6.1 (HR =0.75; *P*=0.0026; 7.5 mg) (HR =0.82; *P*=0.03; 15 mg)	NA
Barlesi et al[78]		Bevacizumab (125) Bevacizumab + pemetrexed (128)	3.7 versus 7.4 (HR =0.48; *P*<0.001)	NA
Zhou et al[79]		CbP + bevacizumab (138) CbP (138)	9.6 versus 6.5 (HR =0.40; *P*<0.001)	24.3 versus 17.7 (HR =0.68; *P*=0.0154)
Pujade-Lauraine et al[80]	ROC	Paclitaxel + PLD/topotecan + bevacizumab (179) Paclitaxel + PLD/topotecan (182)	6.7 versus 3.4 (HR =0.48; *P*<0.001)	NS
Aghajanian et al[81]		GC + bevacizumab (242) GC + placebo (242)	12.4 versus 8.4 (HR =0.484; *P*<0.0001)	NS
Ohtsu et al[82]	GC/GEJ	Fluoropyrimidine–cisplatin + bevacizumab (387) Fluoropyrimidine–cisplatin + placebo (387)	6.7 versus 5.3 (HR =0.80; *P*=0.0037)	12.1 versus 10.1 (HR =0.87; *P*=0.1002)
Wilke et al[83]		Paclitaxel + ramucirumab (330) Paclitaxel + placebo (335)	4.4 versus 2.9 (HR =0.635; *P*<0.0001)	9.6 versus 7.4 (HR =0.807; *P*=0.017)

Abbreviations: CRC, colorectal cancer; NSCLC, non-small-cell lung cancer; ROC, recurrent ovarian, primary peritoneal, or fallopian tube cancer; GC/GEJ, gastric cancer/cancers of the distal esophagus and gastroesophageal junction; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; OS, overall survival; NS, not significant; NA, not available; HR, hazard ratio; CbP, carboplatin plus paclitaxel; CG, cisplatin plus gemcitabine; GC, gemcitabine plus carboplatin.

cediranib-containing regimens treatment had improved overall survival.[63] These data strongly indicate that vascular normalization hypothesis theoretically and practically improves anomalous tumor vascular state. It makes the blood flow more uniform with subsequent increased uptake of cytotoxic drugs and oxygen, which result in better combined treatment outcome. There is no denying that "vascular normalization" theory is not universally recognized. A study indicated a rapid and significant reduction in perfusion and uptake of docetaxel in non-small-cell lung cancer after administration of bevacizumab.[64] However, this study did not look at the time course of perfusion or drug uptake and did not concern the patients' survival benefit after treatment. Meanwhile, these patients were treated with the single dose of 15 mg/kg, and this study also did not examine whether a lower dose of bevacizumab had a diverse result. Thus, the optimal dose and scheduling of anti-VEGF agents are not yet clearly defined for the combined regimens in cancer patients. A crucial need remains for substantial research of therapeutic regimen and individual heterogeneity to support the vascular normalization theory.

The hypothesis

Given the fact that hypercoagulabale state and aberrant angiogenesis play significant roles in tumor microenvironment, we proposed combining two therapeutic strategies, anticoagulant and antiangiogenic therapy, to improve tumor patient prognosis by enhancing vessel perfusion, drug delivery, and oxygenation (Figure 1). As is shown earlier, inadequate intratumor perfusion could mainly result from two aspects. On one hand, intravascular and extravascular thrombi reduce effective cross-sectional area of tumor blood vessels. On the other hand, vessel hyperpermeability and tortuosity reduce blood flow rates in tumors because of excessive fluid loss and vessel resistance. Thus, anticoagulation strategy is based on the following progression of occurrence: solve previously existing thrombi, alleviate stress levels, enlarge vessel diameter, reopen restricted vessels, improve perfusion, and maximally result in enhanced drug delivery and oxygenation. Furthermore, the significant role of prevention and treatment of cancer-associated thrombosis and potential anticancer effects necessitates applying anticoagulant therapy clinically. Vascular normalization

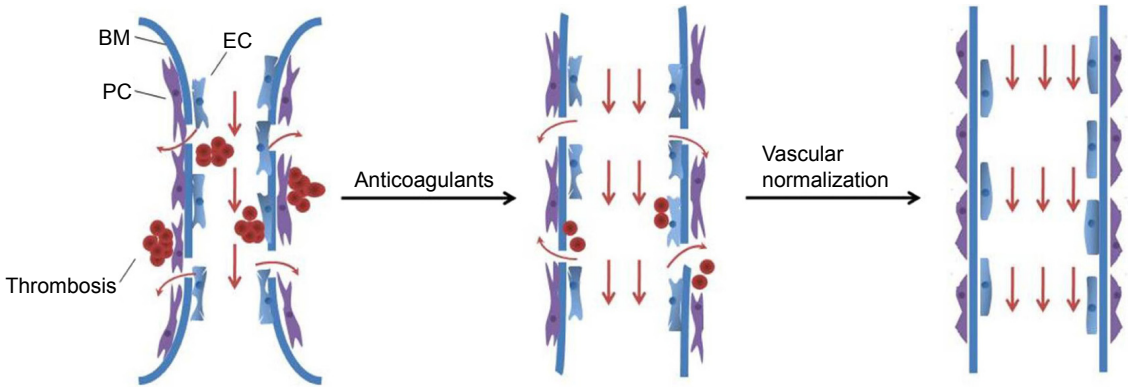

Figure 1 Strategies to enhance blood vessel perfusion and drug penetration.
Notes: Anticoagulant treatment depletes the deposition of fibrin or other plasma proteins on the blood vessel wall and the extravascular thrombosis, which increases the effective cross-sectional area of tumor blood vessels and improves perfusion. Vascular normalization remodels tumor vessels, which decreases vessel permeability and improves perfusion. Both strategies can be applied either alone or in combination based on whether tumor blood is hypercoagulable, vessels are aberrant, both of these, or neither.
Abbreviations: EC, endothelial cell; BM, basement membrane; PC, pericyte.

alters the monstrous vasculature phenotype to a relatively functional phenotype, as normal blood vessels. By using judicious dose and scheduling of antiangiogenic agents, tumor vessels restore relatively mature hierarchical structure and reduce blood content leakiness. Consequently, the interstitial fluid pressure and blood viscosity are recovered, which increase drug delivery and oxygen transport. However, the vascular normalization effect is transient. Unreasonable application of anti-VEGF treatment, including larger dose or longer duration, may destroy present vascular system, generate compensatory angiogenesis signaling pathways, and even facilitate primary tumor dissemination to distant organs.[65,66] In brief, anticoagulant and antiangiogenic therapy alleviate the problem of tumor perfusion abnormity from respective angles. Anticoagulant therapy improves abnormal high-coagulate blood, while antiangiogenic therapy modifies aberrant angiogenesis by vascular normalization. Thromboembolic events, especially arterial thrombosis, are remarkable adverse effects of VEGF inhibitors. A pooled analysis of five randomized trials indicated that addition of bevacizumab to chemotherapy was associated with a twofold increase in arterial thromboembolic events (ATEs) compared with chemotherapy alone (3.8% vs 1.7%; P=0.031). The enhancement was further aggravated in elderly patients or those with a history of ATEs.[67] Thus, it is acceptable to use anticoagulant drugs as standard care in reducing the risk of ATEs in terms of VEGF inhibitors. Notably, the risk of bleeding is raised in patients treated with both anticoagulant and VEGF-targeted drugs.[68] The hemorrhage symptoms range from moderate mucocutaneous bleeding to fatal tumor-related bleeding. Combining the two agents with chemotherapy can further increase the incidence and severity of bleeding events. It is essential that each patient should undergo elaborate risk–benefit assessment and management.Particular attention must be paid to those patients with risk factors, or with a history of bleeding. The effective benefit of the two strategies depends on the tumor microenvironment and particularly on whether tumor blood is hypercoagulable, vessels are aberrant, both of these, or neither. Thus, the paradigms that underlie anticoagulant and vascular normalization strategies are still open for improvement. We should consider the pathological process of tumor cells of every patient.

Conclusion

The tumor microenvironment is entirely antithetical to normal tissues, characterized by prothrombotic state, monstrous vasculature structure, and low perfusion rates. In order to gain better oncotherapy efficiency, we need to get the abnormal tumor microenvironment back on track. In this article, we hypothesized that two complementary therapeutic strategies, the recuperation of hypercoagulabale state with anticoagulant therapy and the normalization of the tumor vessel with anti-VEGF agents, may be ideal candidate methods that normalize the tumor microenvironment. Though the direct evidence in support of therapeutic benefits of vascular normalization and anticoagulation in cancer is insufficient, it provides a novel perspective into the complex pharmacokinetic and pharmacodynamic impact and interactions between hemodynamics and antitumor agent transportation. Thus, many questions remain to be explained, and more preclinical evidence is needed to support the paradigm. Scientific guidelines for the judicious application of these therapeutic strategies are necessary, given the high heterogeneity of patient constitution,

tumor nature, and the differences between primary tumors and metastases. We hope that this new strategy could yield a breakthrough that results in fluent tumor vessel perfusion and drug delivery and finally improves the outcomes of cancer patients.

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Disclosure

The authors report no conflicts of interest in this work.

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