



[haematologica reports]
2005;1(9):40-42

Vascular complications of endothelium targeting therapies

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Tumor vasculature and neoangiogenesis have recently become promising targets for antineoplastic therapy. Antiangiogenic agents act by preventing the formation of new vessels, while vascular targeting drugs cause a selective damage of already formed tumor blood vessels. In order to maintain their efficacy, antiangiogenic compounds need to be administered continuously. They are mainly used in association with standard chemotherapies, raising a critical question about their safety and toxicity, as shown by the first clinical trials with these agents, in which thrombotic or hemorrhagic events emerged as important complications.

Incidence of vascular complications

Venous thromboembolism (VTE) has emerged as a frequent complication in multiple myeloma patients treated with thalidomide, especially in combination with doxorubicin-containing regimens (VTE rate of 34% in newly diagnosed patients).¹ Although the precise mechanism of thalidomide efficacy is not known, this drug was shown to have antiangiogenic effects. In other malignancies, a high rate of thrombotic complications was also reported, in particular when the drug was administered in association with chemotherapy (43% VTE when combined with gemcitabine and fluorouracil in metastatic renal cancer).²

VTE was also observed with other antiangiogenic agents associated with chemotherapy (see Table 1).

SU5416, an inhibitor of vascular endothelial growth factor receptor-1 and -2, showed an incidence of VTE from 5% when used as a single agent (145 mg/m² twice weekly) in patients with advanced solid cancers³ to 11% in another study including 36 patients with hormone-refractory prostate cancer.⁴

In this second study, one patient developed pulmonary embolism, one deep vein thrombosis (DVT), one sinus vein thrombosis and one had a cerebrovascular accident.

Incidence of VTE was low with the use of SU5416 as single agent in patients with hematologic malignancies (6% in patients with refractory myeloproliferative diseases).⁵

However, VTE was shown to be a relevant complication in a Phase 1 study using the combination of gemcitabine, cisplatin and SU5416 in an escalating dose schedule for patients with solid tumors.⁶ At the dose of 145 mg/m², 5/13 patients (38%) developed VTE. Subsequently, when the dose was reduced to 85 mg/m², three other thromboembolic events occurred, including pulmonary embolism in one case. Because of the high incidence of vascular complications, the study was terminated.

In the case of bevacizumab, a recombinant humanized monoclonal antibody (rhuMAb) targeting VEGF, both thrombotic and bleeding complications were observed, but a clear association of these toxicities with the agent has not been established. In a Phase I study using rhuMAb in patients with advanced solid malignancies, two episodes of intratumor serious bleeding were reported, but they were considered related to their underlying disease.⁷ A Phase 2 trial of bevacizumab in patients with metastatic renal cancer showed a higher incidence of epistaxis and hematuria in the high-dose (bevacizumab 10 mg/kg) arm compared to placebo.⁸

Bleeding and thrombotic complications occurred at an increased incidence in the bevacizumab arms (5 mg/kg and 10 mg/kg) of a Phase 2 study comparing the combination of fluorouracil and leucovorin, with or without bevacizumab, in patients with metastatic colorectal cancer.⁹ Mild epistaxis related to bevacizumab seems to be common, but a significant higher incidence of more severe bleeding or thromboembolism was not confirmed in a Phase 3 trial including 813 patients with metastatic colorectal cancer, randomized to receive irinotecan, fluorouracil and leucovorin with or without bevacizumab.¹⁰ When these data were analyzed together with pooled raw

Table 1. Incidence of thromboembolic events during treatment with antiangiogenic agents.

Therapy	Thromboembolic events	Reference
Thalidome/dexamethasone (newly diagnosed patients)	26%	Cavo <i>et al.</i> , 2002
Thalidomide+chemotherapy (newly diagnosed patients)	34%	Zangari <i>et al.</i> , 2004
SU5416	11%	Stadler <i>et al.</i> , 2004
SU5416	6%	Giles <i>et al.</i> , 2003
SU5416 (145 mg/m ²)+cisplatin and gemcitabine	38%	Kuenen <i>et al.</i> , 2002
Bevacizumab (5 mg and 10 mg/Kg)+ fluorouracil and leucovorin	19%	Kabbinavar <i>et al.</i> , 2003
Angiostatin	8%	Beerepoot <i>et al.</i> , 2003
Squalamine lactate + carboplatin and paclitaxel	7%	Herbst <i>et al.</i> , 2003

data from two other similar trials, no increase in thromboembolic or severe bleeding events was reported.¹¹ For other antiangiogenic factors, only few hemorrhagic or thrombotic events have been reported. No significant VTE has been reported so far in clinical trials with other antiangiogenic compounds controlling activation and growth of endothelial cells or the interactions with the matrix, suggesting that these complications are related to the specific mechanism of some drugs rather than to a general inhibition of angiogenesis.

Antiangiogenic activity and thrombosis

It seems reasonable to ascribe the thrombotic complications during antiangiogenic therapy to the capability of these agents to produce endothelial dysfunction, which can lead to thrombosis when associated with other physical or chemical stress. An alternative hypothesis, suggested by Kuenen and Giaccione, is that compounds interfering with the VEGF signaling pathway make endothelial cells more vulnerable and, probably, procoagulant when apoptosis is induced and subendothelial tissue factor is exposed to blood. In a pharmacokinetic study of SU5416 in patients with solid tumors⁶ thrombin/antithrombin complexes (TAT complexes), prothrombin activation fragment F1+2 and endogenous thrombin potential (ETP) were measured in three patients who developed DVT. They exhibited a clear increase of TAT complexes, F1+2 and ETP in a cycle-dependent manner, suggesting that it was caused by cytostatic drugs rather than by SU5416. S-E-selectin (soluble E-selectin), VWF

and TF showed a similar cycle-dependent pattern. Repeating the same tests in patients treated with different drug combinations, the authors concluded that SU5416 alone can induce endothelial cell activation whereas cisplatin and gemcitabine (CG) alone induce an activation of the coagulation cascade; using SU5416 in combination with CG, both pathways are activated.¹²

They also showed that changes in s-E-selectin levels can predict activation of coagulation (F1+2). In addition, the fall in platelet count was correlated with increased level of s-E-selectin, suggesting that cytotoxic agents-induced thrombocytopenia could enhance the toxicity to endothelial cells by depriving them of platelet-carried VEGF.

Recently, it has been shown that a fibrinogen-derived peptide, α statin, has potent antiangiogenic properties *in vitro* and can also inhibit tumor growth in a murin model. Interestingly, this peptide targets tumor blood vessels, causing endothelial cell damage, fibrin deposition and thrombosis, but no effect was seen in normal vessels, indicating the presence of selective toxicity on tumor vasculature.¹³

These findings suggest that multiple and complex interactions occur between tumor cells, endothelial cells, plasma and local factors modulating angiogenesis and thrombosis. It is not possible to predict the effect of a chemotherapy/antiangiogenic agent combination until all mechanisms will be clarified. Therefore, well conducted clinical studies are required to analyze all therapeutic and toxic properties of these new promising compounds.

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