Therapeutic Options in Patients with DIC and Cancer

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Introduction

Malignant disease may be complicated by the occurrence of disseminated intravascular coagulation (DIC) in 7–20% of cases [1]. In particular, adenocarcinoma and hematological malignancies are relatively frequently complicated by DIC [2, 3]. Clinically, DIC in cancer has in general a less fulminant presentation than the types of DIC complicating sepsis and trauma. A more gradual, but also more chronic, systemic activation of coagulation can proceed subclinically [4]. The manifestation of DIC may be merely thrombotic, with obstruction of the microvasculature of various organs but more frequently venous thromboembolism occurs [5]. Although the pathogenesis of DIC in patients with cancer follows similar pathways as in other underlying causes of DIC, some pathogenetic features are quite specific for malignant diseases [6, 7]. In the following, a brief overview of the pathogenesis of DIC in cancer will be given, with an emphasis of those pathways that provide a point of impact for (supportive) treatment strategies in patients with cancer and DIC.

Pathogenesis of DIC in Cancer

Malignant cells can express different procoagulant molecules including tissue factor (TF), which assembles with factor VII(a) to activate factors IX and X, and subsequently

generates thrombin, which converts fibrinogen into fibrin, activates platelets and further amplifies the coagulation cascade [8, 9]. Previous studies have shown the occurrence of functionally active tissue factor in vascular endothelial cells as well as tumor cells in breast cancer, while not appearing in material from patients with benign fibrocystic breast disease [10]. It should be noted that the role of tissue factor in pathophysiology is only partly understood as yet. Independent from its clotting cofactor function tissue factor appears to be involved in tumor metastasis and angiogenesis, factors that may directly influence the course of malignancy and affect the occurrence of thrombosis [11]. Another, more cancer-specific procoagulant that is expressed by tumor cells is cancer procoagulant (CP), a cysteine protease with factor X activating properties [12]. Cancer procoagulant is an endopeptidase that is found in extracts on neoplastic cells but also in the plasma of patients with solid tumors. The exact role of CP in the pathogenesis of cancer-related DIC is unclear.

Another factor in the procoagulant state associated with cancer may be a downregulation of physiological anticoagulant pathways [13]. Experimental studies have shown that anticoagulant concentrates may affect coagulation but also tumor growth and metastasis formation [14]. Also, a marked increase in resistance towards activated protein C was observed in patients with cancer [15]. Lastly, a disbalance between tissue factor expression and its main inhibitor, tissue factor pathway inhibitor (TFPI) may also

affect the procoagulant state in cancer [16]. In addition, another mechanisms by which tumor cells may contribute to the pathogenesis of DIC is by expressing fibrinolytic proteins [17]. Despite the ability of many malignant cells to express plasminogen activators, such as urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA), most tumors induce a hypofibrinolytic state. Since DIC is commonly characterized by a shut-down of the fibrinolytic system (mostly due to high levels of the fibrinolytic inhibitor PAI-1) this may represent an alternative mechanism for the development of DIC in cancer.

Potential Therapeutic Consequences

In view of the central role of tissue factor in the pathogenesis of the procoagulant state in cancer, therapies directed against tissue factor activity might be effective. In experimental settings the efficacy of TFPI in blocking

tissue factor-mediated thrombin generation, but also on tumor seeding and growth, has been demonstrated [14]. Another point of impact might be the activated protein C pathway. Activated protein C is a pivotal inhibitor of coagulation but has in addition a number of other effects in the microvasculature, including a modulating effect on inflammation [18]. In cancer patients there is a remarkable upregulation of the endothelial protein C receptor (EPCR), which plays a role in these effects of activated protein C [19]. Treatment targeted at the protein C system, either by infusion of recombinant activated protein C or by modulating the expression or binding capacity of EPCR might prove beneficial in containing the activation of coagulation in cancer, and may have additional effects on the tumor and its dissemination. Adequate clinical studies with either TFPI or activated protein C in patients with cancer are not available at this time and are required to assess the role of modulation of coagulation in patients with malignant disease.

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