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Disseminated intravascular coagulation in cancer patients

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Disseminated intravascular coagulation (DIC) is a syndrome that may complicate a variety of diseases, including malignant disease. DIC is characterized by widespread, intravascular activation of coagulation (leading to intravascular fibrin deposition) and simultaneous consumption of coagulation factors and platelets (potentially resulting in bleeding). 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. Eventually, this process may lead to exhaustion of platelets and coagulation factors, and bleeding (e.g. at the site of the tumour) may be the first clinical symptom indicating the presence of DIC. In some cases, the clinical presentation of DIC in cancer may be reminiscent of thrombotic microangiopathies, which is understandable in view of the role of the endothelium in both conditions. The therapeutic cornerstone of DIC is treatment of the underlying disorder, but supportive treatment specifically aimed at the haemostatic system may be required.

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In clinical medicine, there is a tight relationship between the presence of malignant disease and the occurrence of thrombosis. Patients with cancer have an increased risk of venous thromboembolism (VTE), which may even be the first clinical manifestation of the malignancy. However, the thrombotic complications of cancer are not limited to VTE, since other manifestations of the prohaemostatic state, in its most extreme form appearing as disseminated intravascular coagulation (DIC), may also occur [1–3]. A specific presentation of cancer-related coagulopathy that is often difficult to distinguish from DIC is thrombotic microangiopathic disease [4].

The mechanisms that lead to activation of coagulation and the ensuing procoagulant state in cancer are largely understood. There are pivotal roles for tissue factor (TF)- and cancer-procoagulant-mediated

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activation of coagulation, cytokine-regulated defective anticoagulant mechanisms and fibrinolytic pathways, and damaged endothelium, which is an important target for chemotherapy. All of these mechanisms may act in concert and will result in various manifestations of thrombotic complications.

Incidence

It is not clear to what extent the manifestation of clinically overt thromboembolism can be ascribed to malignancy-associated DIC. There is ample evidence for a procoagulant state in virtually all patients with advanced malignant disease; however, the incidence of overt DIC appears to be much lower [5]. The incidence of DIC in consecutive patients with solid tumours was found to be 7% in a recent clinical study, and in patients presenting with acute leukaemia, particularly acute lymphoblastic leukaemia, DIC can be diagnosed in 15–20% of patients [6,7]. Some reports indicate that the incidence of DIC in acute leukaemia patients might increase further during remission induction with chemotherapy [8]. In patients with acute promyelocytic leukaemia, DIC may be diagnosed in more than 90% of patients at the time of diagnosis or after initiation of remission induction [9,10].

Pathogenesis

The coagulopathy that accompanies acute promyelocytic leukaemia is often seen as one of the most straightforward forms of DIC complicating malignancy [11]. However, this form of leukaemia-associated haemostatic derangement can be considered as a exceptional type of DIC, characterized by marked hyperfibrinolysis. The clinical presentation of severe bleeding associated with laboratory findings of a low fibrinogen level, very high levels of fibrin split products and fibrinogen degradation products, and massive consumption of plasminogen and α2-antiplasmin (leading to inordinately high levels of plasmin-α2-antiplasmin complex levels) supports that notion [12]. The precise pathogenesis of this hyperfibrinolysis has, however, not been elucidated. Plasma levels of physiological plasminogen activators (such as urokinase-type plasminogen activator and tissue-type plasminogen activator) cannot explain the massive plasminogen activation, nor is a role of leukocytic elastase-mediated hyperfibrinolysis likely. A recent report points to a potential newly described receptor for fibrinolytic proteins, annexin II, that is expressed on the surface of leukaemic cells in patients with acute promyelocytic leukaemia. Annexin II may facilitate plasmin generation at the surface of the cells, and may thereby play a pivotal role in development of the hyperfibrinolytic state. Despite the prominent role of hyperfibrinolysis in patients with acute promyelocytic leukaemia, there is mounting evidence that this derangement is superimposed on a more common presentation of DIC, characterized by coagulation activation and fibrin deposition. Indeed, diffuse thrombosis is found in 15–25% of cases at autopsy, and recent studies have demonstrated tissue-factor-dependent activation of coagulation in this patient category.

Solid tumour cells can express different procoagulant molecules including TF, which binds with factor VII(a) to activate factors IX and X, and cancer procoagulant, a cysteine protease with factor-X-activating properties [13]. Recent studies show the occurrence of TF in vascular endothelial cells as well as tumour cells in breast cancer, while not appearing in material from patients with benign fibrocystic breast disease, and this TF was functionally active [14,15]. It should be noted that the role of TF in pathophysiology is only partly understood. Independent from its clotting cofactor function, TF appears to be involved in tumour metastasis and angiogenesis [16–18]; factors that may directly influence the course of malignancy and affect the occurrence of thrombosis [19]. Cancer procoagulant is an endopeptidase that is found in extracts on neoplastic cells but also in the plasma of patients with solid tumours. The exact role of cancer procoagulant in the pathogenesis of cancer-related DIC is unclear. Another mechanism by which tumour cells may contribute to the pathogenesis of DIC is by expressing fibrinolytic proteins. Despite the ability of many malignant cells to express plasminogen activators, such as urokinase-type plasminogen activator and tissue-type plasminogen activator, most tumours induce a hypofibrinolytic state. Since DIC is commonly characterized by a shut-down of the fibrinolytic system (mainly due to high levels of the fibrinolytic inhibitor, plasminogen activator inhibitor type 1 (PAI-1)], this may represent an alternative mechanism for the development of DIC in cancer.

Cellular factors presumably precipitate coagulation activation in patients with, in most cases, solid tumours. In addition, in a series of patients with malignant neoplasms, high endothelin plasma levels correlated well with progression of DIC, suggesting that this protein may influence the development of DIC in cancer [20].

Virtually all pathways that contribute to the occurrence of DIC are driven by cytokines. Interleukin-6 (IL-6) has been identified as one of the most important pro-inflammatory cytokines that is able to induce TF expression on cells. Indeed, inhibition of IL-6 results in inhibition of endotoxin-stimulated activation of coagulation. In contrast, changes in fibrinolysis and microvascular physiological anticoagulant pathways are mainly dependent on tumour necrosis factor-α. Other cytokines that participate in the systemic activation of coagulation are IL-1β and IL-8, whereas anti-inflammatory cytokines, such as IL-10, are able to inhibit DIC. Since many types of tumour have the ability to synthesize and release cytokines or to stimulate other cells to activate the cytokine network, it is likely that cytokine-dependent modulation of coagulation and fibrinolysis plays a role in cancer-related DIC.

Chemotherapy may enhance the risk of thrombosis due to its damaging effect on the endothelium. Anti-angiogenic agents, particularly in combination with conventional chemotherapy, may increase this risk. Administration of thalidomide in combination with chemotherapy (and possibly in combination with steroids) in patients with renal cell carcinoma or multiple myeloma results in a very high rate of thrombosis (43% and 28% of patients, respectively) [21,22]. New-generation anti-angiogenic agents have been associated with a high risk of VTE and also arterial thromboembolism, presumably due to their effect on the endothelium [23,24].

Indwelling catheters may form a template for thrombosis in patients with cancer, and this risk seems to be greater when catheter-related infection occurs. Retrospective studies estimate the risk of symptomatic catheter-associated thrombosis to be 4–15% [25,26]. A recent trial, however, showed a much lower incidence of (venographic) thrombosis in patients with a haematological malignancy and no effect of prophylaxis with low-molecular-weight heparin [27].

Clinical presentation and diagnosis

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. Eventually, this process may lead to exhaustion of platelets and coagulation factors, and bleeding (e.g. at the site of the tumour) may be the first clinical symptom indicating the presence of DIC. If liver function is not compromised, enhanced synthesis of coagulation proteins may mask the ongoing consumption of factors, and in that case, thrombocytopenia is the most prominent sign of ongoing DIC. Measurement of fibrin-related markers (such as soluble fibrin or fibrin degradation products) may be helpful in establishing the diagnosis in a routine setting; however, the specificity of these tests in cancer-related DIC has not been established to date.

Microangiopathy in cancer

DIC in patients with cancer may be difficult to discriminate from overt DIC in this setting [28]. Since bone marrow toxicity of (high-dose) chemotherapy may be overcome by the use of autologous or allogeneic stem cell support and more intensive treatment regimens are adopted, other types of chemotherapy-related organ toxicity appear to occur more frequently. Thrombotic microangiopathy is one such serious complication that may occur in an increasing number of patients following high-dose chemotherapy in combination with autologous or allogeneic stem cell transplantation [29,30]. In recent years, more than 200 cases have been reported in up to 30 publications, and initial prospective (laboratory-based) studies indicate that the incidence of the syndrome ranges from 2% to 8% of patients that receive high-dose chemotherapy [31–35]. Thrombotic microangiopathy encompasses a number of syndromes which closely resemble each other, such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura (TTP). Also, some features of veno-occlusive disease are similar to those observed in thrombotic microangiopathy. These syndromes are characterized by platelet adhesion to endothelial cells, followed by massive platelet aggregation and activation (resulting in consumptive thrombocytopenia), subsequent activation of the coagulation system leading to fibrin formation and

deposition, and inadequate fibrin removal due to impaired function of the fibrinolytic system. The formed thrombi in the (micro) vasculature causes impaired organ function (leading, for example, to renal or hepatic insufficiency) and red cell fragmentation due to microangiopathic haemolysis. Remarkably, the condition generally arises 2–9 months after cessation of chemotherapy, when the cancer itself is in remission. Historically, the syndrome appeared to be restricted to specific types of antineoplastic chemotherapy, such as mitomycin-C, but now many different types of chemotherapy have been associated with the occurrence of thrombotic microangiopathy [30,36]. The dose of chemotherapy appears to be of importance, which explains the increasing incidence of the syndrome since the widespread clinical application of stem cell transplantation (bone marrow transplantatation or peripheral stem cell transplantation) enables the use of much higher doses of chemotherapy. Furthermore, simultaneous total body irradiation and the use of cyclosporin A are associated with a higher incidence of postchemotherapy thrombotic microangiopathy [33,37]. The prognosis for this particular complication of high-dose chemotherapy is poor. Mortality of all affected patients was 31% and mortality related directly to thrombotic microangiopathy was 23% [35]. In addition, survivors may suffer from persistent or even progressive renal insufficiency.

The pathogenesis of thrombotic microangiopathy remains to be elucidated. It may be hypothesized that endothelial toxicity of chemotherapy plays a central role in development of the syndrome. Endothelial damage and subsequent dysfunction have been implicated in various reports dealing with chemotherapy-related thrombotic microangiopathy; however, there is no definitive proof for this hypothesis, nor is it clear how endothelial dysfunction may result in thrombotic microangiopathy. Detailed insight in the various pathogenetic processes is required in order to devise rational strategies for treatment or prophylaxis of this complication.

A pivotal role of endothelium in cancer-related DIC and thrombotic microangiopathy?

Vascular endothelium plays a central role in the processes of haemostasis, coagulation and fibrinolysis. Endothelial cells are the primary source of von Willebrand factor, which is the adhesive protein responsible for interaction of the vessel wall with glycoprotein Ib receptors on the platelet surface. In thrombotic microangiopathy, increased plasma levels of von Willebrand factor are found [37,38], potentially contributing to the initiation of platelet activation. In-vitro studies have shown that chemotherapy enhances endothelial cell reactivity to platelets, mediated by cytokine-induced expression of endothelial adhesion molecules [39]. Also, endothelial cells may express TF (the main initiator of coagulation) and thrombomodulin (which modulates the activation of protein C, an important physiological inhibitor of the coagulation system) on their surface [40]. Defective regulation of TF and/or thrombomodulin expression on endothelial cells may result in facilitated thrombin generation, leading to fibrinogen to fibrin conversion and further enhancement of platelet activation. In addition, endothelial cells synthesize, store and release both tissue-type plasminogen activator and urokinase-type plasminogen activator, and the main inhibitor of fibrinolysis, PAI-1 [41]. Dysfunction of endothelial cells results in impaired fibrinolysis and may lead to the inadequate removal of fibrin depositions. Finally, a whole series of adhesion molecules, expressed by endothelial cells, can mediate the binding and activation of white blood cells to the endothelium, resulting in the release of various cytokines that are able to induce activation of blood coagulation and depression of fibrinolytic function [42].

Amongst other agents that were found to be toxic for endothelial cells, cyclosporin A has been studied extensively. The observation that simultaneous treatment with cyclosporin may aggravate chemotherapy-induced thrombotic microangiopathy further strengthens the hypothesis that damage to the endothelium by chemotherapy is the pivotal process in the pathogenesis of this syndrome.

Endothelial cells synthesize and release von Willebrand factor, which plays an important role in platelet adhesion to the vessel wall. Damage to the endothelium is associated with an increase in circulating von Willebrand factor. Indeed, in a recent study, increased plasma levels of von Willebrand factor were found in cancer patients who developed thrombotic microangiopathy [43]. The multimeric pattern of von Willebrand factor determines its biological activity, i.e. high-molecular-weight von Willebrand multimers are functionally more potent than other forms of von Willebrand factor. Remarkably, in 'conventional' TTP and haemolytic uraemic syndrome in particular, high-molecular-weight multimers of von Willebrand factor are found, which may contribute to the

increased platelet reactivity observed [33]. Reports on the multimeric pattern of von Willebrand factor in cancer and after high-dose chemotherapy are controversial [44,45]. A recent study found reduced levels of the von Willebrand cleaving protease ADAMTS-13 in patients with cancer [46].

Endothelial cells are also important for the regulation of blood coagulation because of the expression of both procoagulant and anticoagulant mediators [42]. It has been shown that cytokine-activated endothelial cells in cancer patients show enhanced TF expression and TF-dependent pro-coagulant activity [47]. Patients with 'conventional' TTP show enhanced levels of TF antigen in blood [48]. There are no published data on the effect of chemotherapy on TF expression on endothelial cells of patients with cancer. In addition, the main regulator of the TF pathway, TF pathway inhibitor (TFPI), is also present on the surface of endothelial cells. Reduction in TFPI activity results in enhanced thrombin generation in vitro and in experiments of experimental coagulation activation in vivo. Damage to endothelial cells may result in loss of TFPI on the endothelial cell surface and it has been shown that plasma levels of TFPI are decreased in patients with TTP. There are no data available on TFPI activity in patients with cancer or chemotherapy-induced thrombotic microangiopathy. In conclusion, there is evidence that the TF pathway and its inhibitor may play an important regulatory role in chemotherapy-induced thrombotic microangiopathy.

Another important role of endothelial cells in the regulation of blood coagulation is by means of thrombomodulin expression on its surface [49]. After (thrombin-mediated) activation of thrombo-modulin at the endothelial surface, circulating protein C is converted to activated protein C and may act as an important inhibitor of blood coagulation, due to proteolytic degradation of the co-factors V and VIII. The central role of the protein C system in the regulation of blood coagulation is illustrated by the occurrence of thrombotic disease in patients with a defective protein C system. It has been shown in vitro that endothelial cells may react to certain stimuli such as toxic substances or cytokines with downregulation of thrombomodulin expression, thereby reducing the formation of activated protein C and blocking this inhibitory pathway [49]. It is likely that these mechanisms are also operational in cancer patients. The use of high-dose chemotherapy has been associated with impaired function of the protein C system; however, the mechanism has not been elucidated.

Lastly, endothelial cells are the principal site of production, storage and release of fibrinolytic activators, i.e. tissue-type plasminogen activator and urokinase-type plasminogen activator. Impaired release of plasminogen activators from the endothelium results in a reduction in fibrinolytic activity in vivo and may contribute to the pathogenesis of pathological thrombus formation. In addition, endo-thelial cells may produce PAI-1, the main inhibitor of plasminogen activation, and it has been shown in vitro that activation of endothelial cells results in enhanced production and release of this inhibitor of fibrinolysis. Elevated levels of PAI-1 are associated with the occurrence of thrombotic disease [50]. Recent reports indicate that endothelial damage may result in endothelial dysfunction, leading to impaired release of plasminogen activators and increased levels of PAI-1, thus resulting in an overall antifibrinolytic state [51]. For example, it has been shown that cyclosporin-A-induced damage to endothelial cells results in a reduction of fibrinolytic activity caused by this mechanism. In cancer patients with TTP, a similar pattern has been shown regarding fibrinolytic activation and inhibition: impaired release of plasminogen activators and enhanced levels of PAI-1 [52]. There are only limited data in the literature regarding endothelial function as related to fibrinolysis after treatment with high-dose chemotherapy [52]; however, on the basis of the above mentioned observations, it may be hypothesized that chemotherapy-induced endothelial injury results in an antifibrinolytic condition which may contribute to the pathogenesis of thrombotic microangiopathy.

Management

The therapeutic cornerstone of DIC is treatment of the underlying disorder. In fact, if the malignant disease can be brought into remission, the DIC will usually disappear simultaneously.

Supportive therapy may consist of anticoagulant treatment; however, the efficacy and safety of this strategy in cancer patients with DIC has never been studied in sound clinical studies. Based on the notion that DIC is characterized by extensive activation of coagulation, anticoagulant treatment may be a rational approach. Experimental studies have shown that heparin can, at least partly, inhibit the activation of coagulation in DIC [53]. There are no clinical randomized controlled trials demonstrating

that the use of heparin in patients with DIC results in an improvement of clinically relevant outcomes. Small, uncontrolled studies have shown that (low-molecular-weight) heparin is capable of improving laboratory abnormalities associated with DIC [54–56]. Patients with DIC (and, in particular, those with cancer) are at high risk of VTE due to the cancer itself and additional factors, including advanced age, recent surgery, immobilization, indwelling vascular catheters and previous VTE history [57]. Therefore, VTE prophylaxis using unfractionated heparin or low-molecular-weight heparin has become the standard of care in patients with cancer and DIC [58,59].

Low levels of platelets and coagulation factors may increase the risk of bleeding. However, plasma or platelet substitution therapy should not be instituted on the basis of laboratory results alone, but are only indicated in patients with active bleeding and in those requiring an invasive procedure or otherwise at risk for bleeding complications. The threshold for transfusing platelets depends on the clinical situation of the patient. In general, platelet transfusions are administered to patients who bleed and who have a platelet count of $<50 \times 10^9$/L. In non-bleeding patients, a much lower threshold for platelet transfusion is used (usually <10–20×10^9/L), which is based on randomized controlled trials in patients with thrombocytopenia following chemotherapy [60].

Based on the notion that depression of the protein C system may contribute significantly to the pathophysiology of DIC, supplementation of activated protein C may be of benefit. Indeed, in experimental sepsis studies, activated protein C was shown to be effective in reducing mortality and organ failure [61]. The clinical efficacy of activated protein C in severe sepsis was demonstrated in a large randomized controlled trial [62]. The role of restoring defective physiological anticoagulant pathways (e.g. by administration of antithrombin or activated protein C concentrates) in patients with cancer has not been evaluated to date.

In patients with severe bleeding, antifibrinolytic treatment may be considered [63]. In fact, since fibrin deposition, partly due to insufficient fibrinolysis, is an important feature of DIC, further inhibition of the fibrinolytic system does not seem appropriate. An exception may be made in those rare cases when primary or secondary hyperfibrinolysis dominates the clinical picture. This is the case in the coagulopathy associated with acute promyelocytic leukaemia, and in some cases of DIC secondary to malignancies (e.g. prostate carcinoma). Uncontrolled observations and one randomized controlled clinical trial have shown the beneficial effect of antifibrinolytic agents in this situation [64]. There are some anecdotal reports of the successful use of recombinant factor VIIa in cancer patients with DIC and life-threatening bleeding, but the efficacy and safety of this treatment in DIC is unknown [65–67].

Practice points

- DIC is a complication of various types of malignant disease
- the clinical presentation of DIC in malignancy is usually less fulminant and follows a more gradual and chronic pattern
- both bleeding and (micro- or macrovascular) thrombosis may be a consequence of DIC in cancer patients
- the pathogenesis of DIC in malignancy follows similar patterns as DIC in other underlying disorders
- there is overlap between DIC and thrombotic microangiopathies in patients with cancer, and both clinical presentation and pathogenesis may be difficult to distinguish

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Research agenda

- the optimal diagnostic approach and clinical management strategy in patients with DIC and cancer needs to be determined
- the effects of cancer treatment on incidence and severity of DIC need further research

Conflict of interest statement

The author has no conflict of interest.

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