Prevention of disseminated intravascular coagulation in cancer

Disseminated intravascular coagulation (DIC) is a syndrome that may complicate a variety of diseases, including malignant disease. DIC is characterized by a widespread and intravascular activation of coagulation (leading to intravascular fibrin deposition) and simultaneous consumption of coagulation factors and platelets (potentially resulting in bleeding). 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 pro-coagulant state in virtually all patients with advanced malignant disease, however, the incidence of overt DIC appears to be much lower.

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 (for example at the site of the tumor) may be the first clinical symptom indicating the presence of DIC.

Diagnosis of DIC in cancer

If the function of the liver 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 so far.

A scoring system that uses simple laboratory tests that are available in almost all hospital laboratories has been developed by the subcommittee on DIC of the International Society on Thrombosis and Haemostasis. Initial prospective validation studies show a high accuracy of this scoring system for the diagnosis of DIC. Other analyses show that the DIC scoring system is a strong independent predictor of a fatal outcome in critically ill patients. However, most of this experience is based on patients with sepsis and trauma. The diagnostic accuracy of the diagnostic score in patients with DIC and cancer is matter of study at present. A previously developed, quite similar, Japanese scoring system for DIC shows a reasonable diagnostic performance in patients with DIC and cancer (mostly leukemia).

(Preventive) therapy of DIC in sepsis

The therapeutic cornerstone of DIC is treatment of the underlying disorder. In fact, if the malignant disease can be brought in remission, the DIC will simultaneously disappear. This has for example been shown in patients with acute promyelocytic leukemia but also in other situations where cancer is complicated by DIC. 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. The administration of platelets, plasma or plasma derivatives is only useful in case of bleeding or if there is a high risk of bleeding. The role of restoring defective physiological anticoagulant pathways (e.g. by administration of antithrombin or activated protein C concentrates) has been extensively studied in patients with sepsis and DIC. A large-scale, multicenter, randomized controlled trial to directly address the efficacy and safety of antithrombin showed no significant reduction in mortality of patients with sepsis who were treated with antithrombin concentrate. Interestingly, post-hoc subgroup analyses indicated some benefit in patients who did not receive concomitant heparin, but this observation needs prospective validation. Based on the notion that depression of the protein C system may significantly contribute to the pathophysiology of DIC, sup-
plementation of activated protein C might be beneficial. A phase III trial of activated protein C concentrate in patients with sepsis was prematurely stopped because of efficacy in reducing mortality in these patients. All cause mortality at 28 days after inclusion was 24.7% in the activated protein C group versus 30.8% in the control group (19.4% relative risk reduction). It is, however, not clear whether these interventions will have any significant effect on the coagulopathy associated with cancer.

References