

RECOMMENDATIONS AND GUIDELINES

Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH

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Scope and methodology

The pathogenesis of cancer-associated disseminated intravascular coagulation (DIC) is complex and multifactorial. It could present as a spectrum ranging from clinically asymptomatic, but with laboratory markers of coagulation activation, to the extreme cases of therapy-resistant thrombosis or bleeding [1]. In this guidance, we try to address some practical considerations for this clinical scenario. This statement will provide clinicians with guidance on how best to manage DIC in patients with cancer and offer expert consensus to help decision-making in challenging situations.

The guidance statements in this document are similar to previous ones [2]. The wording 'we recommend' indicates a strong consensus among the panel members, whereby the clinician should consider adopting the practice in most cases. The wording 'we suggest' reflects a weak guidance statement with moderate consensus among the panel members, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients.

Pathophysiological considerations

Disseminated intravascular coagulation is an intermediary mechanism of disease and is always due to an underlying disorder such as malignancy. When dealing with patients with cancer-related DIC, it is useful to consider the different pathogenetic mechanisms that can lead to the different

clinical manifestations. For practical purposes, cancer-related DIC may be considered as presenting in three forms: (i) 'procoagulant', where excess thrombin generated causes thrombosis in microvascular and macrovascular fields, (ii) 'hyperfibrinolytic', where activation of the fibrinolytic system dominates the picture, and (iii) 'subclinical', where the amounts of thrombin and plasmin generated do not cause obvious clinical manifestations but can be reflected in laboratory markers of coagulation or fibrinolysis activation [3]. Clinical presentation of cancer-associated DIC can be with thrombosis or bleeding or both simultaneously (see Table 1).

In the cases of cancer-associated DIC other than the subclinical type, it is relevant to assess the thrombotic risk (and bleeding risk from hyperfibrinolysis) of the cancer and similarly of the patient as the first step. For example, pancreatic cancers or those with adenocarcinoma are at a very high risk of DIC, in a similar way to patients with pelvic malignancy and a concomitant septic abscess. Evaluation for subclinical or procoagulant DIC should also be considered in cancer patients presenting with an acute embolic stroke or peripheral embolic event who are found to have non-infectious thrombotic endocarditis (usually detected by trans-esophageal echocardiogram). A recently developed risk stratification system, the Khorana score, can identify cancer patients at high risk of thrombosis using a combination of easily available clinical and laboratory variables, validated in a prospective study [4,5]. As no predictive score for thrombosis or bleeding has been validated in cancer-associated DIC, an estimation of these risks through the careful evaluation of clinical and laboratory parameters of each individual patient is advisable.

Guidance statement

1 We suggest the DIC associated with cancer to be categorized into three subtypes (i.e. procoagulant, hyperfibrinolytic and subclinical).

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Table 1 Types of cancer-related DIC and their features

	Procoagulant	Hyperfibrinolytic	Subclinical
Predominant types of cancer	Pancreatic cancer, adenocarcinoma	Acute promyelocytic leukemia, metastatic prostate cancer	Many solid cancers
Predominant clinical symptom	Thrombosis	Bleeding	Neither
Different clinical presentations	Features of arterial ischemia, which can manifest as uneven, patchy discoloration of the skin, symptoms of poor digital circulation, cerebrovascular manifestations, peripheral neuropathy and ischemic colitis Venous thrombosis or pulmonary embolism An unusual form of non-infectious endocarditis has been noted to be a manifestation of cancer-related DIC	Widespread bruising, bleeding from mucosal surfaces, central nervous system, lungs, gastrointestinal tract and from sites of trauma Hemorrhage is the most common cause of induction mortality in acute promyelocytic leukemia, while catastrophic bleeding can occur before the diagnosis is made in some cases.	Only laboratory abnormalities, but no obvious clinical symptoms or signs of coagulation activation or fibrinolysis These abnormalities may include thrombocytopenia, hypofibrinogenemia and microangiopathic hemolytic anemia These features may remain long-standing due to the continuous thrombin generation as part of DIC, but may worsen or improve depending on the underlying malignancy
Treatment	That of underlying cancer Anticoagulation with heparin	That of underlying cancer Supportive care with blood products	That of underlying cancer Anticoagulation with heparin

2 We suggest that all patients with cancer-associated DIC should be risk-assessed for the likelihood of thrombosis and bleeding.

Laboratory measurements

Several biomarkers have been identified as potential predictors of thrombosis in cancer patients. In the setting of DIC, elevated leukocyte counts, decreased hemoglobin and elevated D-dimer can be considered as potentially useful, although not very specific [5]. In comparison with high platelet counts, which are a poor prognostic indicator in malignancy-related thrombosis, in the DIC scenario, decreasing platelet count may be more relevant [6]. The platelet count will usually be moderately or markedly reduced in cancer-related DIC, although in the case of an initial increase to very high levels, the reduction would still be in the normal range. This is a crucial observation, because a normal platelet count, despite a profound decrease from a very high level, may often be discounted as unimportant, when it may be the only sign of DIC in some patients with malignancy [6]. In patients with hematological cancers such as acute promyelocytic leukemia (APL), marrow failure and chemotherapy can affect platelet count, and once again, a decreasing trend should be considered a marker of continuing thrombin generation and thus DIC [7].

Although an abnormal coagulation screen is considered part and parcel of DIC, this is not always the case (this was only noted in about 50% of septic DIC) [8]. The prothrombin time (PT) and partial thromboplastin time (PTT) may not be prolonged in patients with cancer-associated DIC, especially with the subclinical form, when coagulation factor levels are only moderately decreased. Activation of the coagulation system by the malignancy

or associated high levels of factor (F) VIII:C can even shorten the PTT initially [9]. At the same time, the large amount of thrombin generated, if unchecked, can lead to consumption of the clotting factors, which is reflected in prolongation of the clotting screen. In a similar fashion, serum fibrinogen levels are very rarely decreased in the procoagulant type of DIC, although in hyperfibrinolytic form, the levels can decrease dramatically and this was noted to be the most common hemostatic abnormality (60%) in one study [8,9]. An abrupt decrease in fibrinogen can be a strong risk factor for bleeding in any type of DIC and threshold values (1.5–2.0 g L⁻¹) have been suggested for replacing fibrinogen to prevent this complication [10]. Causes of prolonged PT and PTT other than DIC should be considered in patients with cancer including liver impairment, vitamin K deficiency, dysfibrinogenemia, paraproteinemias and acquired inhibitors of coagulation factors [11].

Although studies specifically addressing DIC and cancer have not been performed, it may be useful to monitor the D-dimer values as a surrogate marker for excess thrombin generation and fibrinolysis in DIC. The hyperfibrinolytic type is likely to have very high D-dimer values, which can be reduced by appropriate treatment, while the procoagulant type and subclinical forms can have elevation of D-dimers to varying levels [12]. Once again, worsening D-dimers rather than absolute values are crucial for the diagnosis of DIC.

Guidance statement

1 We recommend that patients at risk of developing cancer-related DIC should have a regular blood count and clotting screen, including fibrinogen and D-dimer measurements. The intensity of monitoring could vary from

monthly to daily and should be decided on a case-by-case basis.

- 2 We suggest worsening laboratory parameters (e.g. 30% or higher drop in platelet count) to be considered diagnostic of subclinical DIC in the absence of clinical manifestations.
- 3 We recommend that physicians bear in mind the variations in the laboratory parameters that can exist due to the effects of the underlying malignancy.

Treatment

The management of DIC is complex. Most of the therapeutic measures are surprisingly not based on high levels of evidence. Its prompt recognition is most important and this aspect is stressed by the ISTH-SSC in the consensus statement [10]. Because DIC is an intermediary mechanism of disease and is always secondary to an underlying process, appropriate management of the underlying malignancy is the key goal of treatment. This is exemplified by the good resolution of DIC in patients with APL with early commencement of the induction therapy [13].

Supportive care Because treatment of cancer is an extended process, it may be relevant to provide supportive care in such patients with blood products and related measures based on some threshold values (borne out by expert opinion) [6,10,14].

Guidance statement

- 1 In patients with DIC and active bleeding, we suggest the use of platelet transfusion to maintain the platelet count above $50 \times 10^9 \text{ L}^{-1}$.
- 2 In patients with DIC who are at high risk of bleeding (e.g. surgery or invasive procedures), we suggest that one to two doses of platelets (commonly from five donors or equivalent) are transfused, if the platelet count is less than $30 \times 10^9 \text{ L}^{-1}$ in APL, and less than $20 \times 10^9 \text{ L}^{-1}$ in other cancers.
- 3 In patients with DIC and active bleeding, we suggest transfusion of fresh frozen plasma ($15\text{--}30 \text{ mL kg}^{-1}$) with careful clinical monitoring to decide on dose adjustments. In the case of concerns over volume overload, we suggest the use of prothrombin complex concentrates.
- 4 In actively bleeding cases with persistently low fibrinogen values (below 1.5 g L^{-1}) despite these supportive measures, we suggest transfusion of two pools of cryoprecipitate (whenever available) or fibrinogen concentrate.

Two additional caveats are to be kept in mind in this context. Firstly, the lifespan of transfused platelets and fibrinogen may be very short, especially in patients with vigorous coagulation activation and fibrinolysis [7]. These

patients require frequent blood monitoring to determine the thresholds and need for (further) replacement therapy. In addition, organ impairment such as liver failure can cause decreased platelet and fibrinogen production and function.

Some patients with cancer may have metastatic disease with poor prognosis. In these cases, based on the discretion of the physician and patient preferences, interventions should be tailored to the available resources.

Inhibition of excess thrombin Because the *sine qua non* of DIC is excess thrombin generation, it is logical to think of antithrombotic agents in the management of DIC. Inhibition of the excess effects of thrombin can be carried out by heparin, either unfractionated (UFH) or low-molecular-weight (LMWH) forms, or with the use of anticoagulant factor concentrates [15]. Heparin has been used historically as a management strategy for DIC in different clinical situations. The risk of bleeding has prompted some recommendations to limit its use in highly prothrombotic forms of DIC, especially those associated with solid cancers [16]. In these cases, heparin should be considered as prophylactic therapy in the absence of contraindications such as low platelet count (less than $20 \times 10^9 \text{ L}^{-1}$) or active bleeding [16]. Subclinical types of DIC will also benefit from heparin prophylaxis, although it is best avoided in hyperfibrinolytic DIC [17].

Randomized controlled studies have not specifically addressed the issue of treatment of a new thromboembolic episode in patients with acute leukemia, while in the case of solid tumors therapeutic-dose LMWH administered for 6 months (first month at full dose and 5 months at 75% of full dose) has proved safe and superior to warfarin in preventing recurrence [16]. In view of the high risk of bleeding in patients with hematologic malignancies such as APL, treatment doses of LMWH with frequent monitoring of peak anti-Xa levels has been suggested [13]. Abnormalities in the clotting screen by themselves should not be considered an absolute contraindication in these circumstances, especially in the absence of bleeding. This is because in these circumstances there is a rebalanced hemostasis, where a reduction in anticlotting factors such as natural anticoagulants (which are not measured) is present in tandem with reduction of clotting factors (measured by PT and APTT) [18].

Choice of heparin is another debated issue in this regard. In those with a high risk of bleeding and renal failure, UFH is chosen due to its easier reversibility, while in all other cases, LMWH should be given [6,13]. Monitoring the antithrombotic capacity of UFH using PTT may have problems because this test may already be prolonged due to DIC. In these cases, the use of heparin anti-FXa activity assays as an alternate method for monitoring can be considered. The anticoagulant concentrates trialed in DIC until recently included antithrombin, activated protein C and soluble thrombomodulin, although

there are no trials to support their use in cancer-related DIC.

Other treatments

It would be expected that patients with hyperfibrinolytic DIC may benefit from antifibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid. Although these agents were advocated for the treatment of APL before the routine use of definitive agents such as all-trans retinoic acid, a larger retrospective study did not demonstrate a significant benefit from this therapy, including for the incidence of early hemorrhagic deaths [19]. In addition, the PETHEMA group also did not identify a clear advantage in reducing hemorrhagic incidents with systematic tranexamic acid prophylaxis along with induction therapy, but did note a trend toward higher thrombotic events [20]. For these reasons, the routine use of antifibrinolytic agents in hyperfibrinolytic DIC cannot be recommended and may be deleterious in the other types [21]. However, if therapy-resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered.

The role of recombinant FVIIa in the management of cancer-related DIC remains uncertain. There are occasional case reports in the literature of successful use of this agent, but there are no randomized controlled trials. In addition, thrombotic risks are definitely associated with this treatment [22]. For this reason, the use of this agent cannot be recommended.

Guidance statement

- 1 We recommend appropriate treatment of underlying cancer as the first-line strategy for cancer-related DIC.
- 2 We recommend prophylactic anticoagulation in all patients with cancer-related DIC, except hyperfibrinolytic DIC, in the absence of contraindications. Therapeutic-dose anticoagulation should be used in those who develop arterial or venous thrombosis in this context.
- 3 We recommend against the routine use of tranexamic acid and recombinant FVIIa in patients with cancer-related DIC. If therapy-resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered.
- 4 We recommend regular clinical and laboratory surveillance to assess the improvement or worsening of the patient, to detect the development of complications including organ failure, and to ensure the underlying condition is being adequately treated.

Additional clinical scenarios

The following are complicating situations in cancer-related DIC, where there are no clear-cut recommendations. Different possible approaches are proposed.

1. A new thrombus in patients with severe thrombocytopenia (less than $25\text{--}50 \times 10^9 \text{ L}^{-1}$): (i) platelet transfusions and therapeutic anticoagulation, (ii) intermediate-dose or prophylactic anticoagulation without transfusions or (iii) no anticoagulation unless the site of thrombus is critical (e.g. pulmonary embolism vs. deep vein thrombus) [2].
- 2 Placement of inferior vena cava filter: a temporary filter should only be considered in patients who cannot be anticoagulated but have a proximal lower limb thrombosis that is likely to embolise. In other situations a filter can be deleterious because it can further activate the coagulation system.

Addendum

J. Thachil designed the study, collected the literature, analyzed and interpreted data, and wrote the manuscript. A. Falanga, M. Levi, H. Liebman and M. Di Nisio collected the literature, analyzed and interpreted data, and critically revised the intellectual content.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

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