



Chemotherapy induced changes to fibrin clots properties in lung cancer: is it favorable?

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Patients with cancer are frequently in a hypercoagulable state and the reported incidences of venous thromboembolism (VTE) and arterial thrombosis in patients with cancer are 4–20% and 2–5%, respectively (1-3). In particular, VTE is associated with worse prognosis in patients with cancer (4,5); therefore, extensive investigations have been performed for the development of useful risk assessment models, identification of better VTE biomarkers, and exploration of efficient therapeutic interventions. Type of cancer, such as ovarian and pancreatic cancers, advanced stage, and systemic treatment with hormonal or cytotoxic drugs have been reported as risk factors for cancer associated VTE in several studies (1,3). Furthermore, accumulating evidence has revealed that the underlying molecular mechanisms of cancer associated VTE are orchestrated by many players, including increased leukocyte and platelet counts as well as the release of procoagulant factors, such as tissue factor (TF), from tumor cells and possibly from surrounding stromal cells (1,2,6). Recently, TF has been reported as a biomarker for predicting recurrent VTE in patients with cancer (7).

Treatment related VTE (trVTE) is a serious adverse event and can be life-threatening mostly because it causes pulmonary embolism (PE). Therefore, elucidation of trVTE pathophysiology and clinical translation of this knowledge is paramount. Chemotherapy-induced endothelial damage and increased TF expression by monocytes and macrophages have been proposed as the mechanisms responsible for trVTE (8). A recent study reported that cell-free DNA released from cells damaged by chemotherapy

acts as a novel procoagulant stimulus (9). Specific drugs, including cisplatin, carboplatin, and gemcitabine, have been reported to be associated with a higher incidence of trVTE compared with other drugs. However, whether increased risk of trVTE associated with these drugs is due to the proposed mechanisms and/or other mechanisms remain to be elucidated.

Development of lysis that is resistant to fibrin clots is the final step in coagulation, and its alteration has been demonstrated to be responsible for major thrombotic disorders, such as coronary and peripheral arterial disease (10). Nevertheless, to date, very few studies have examined pathological alterations in trVTE associated fibrinolysis (11,12). Recently, Królczyk *et al.* reported a study in the *Journal of Thoracic Disease* investigating whether 3-month chemotherapy has an impact on the characteristics of plasma fibrin clots in patients with lung cancer (13). In total, 37 patients with small cell lung cancer and 46 patients with non-small cell lung cancer were consecutively enrolled in the study. Various parameters assessing fibrin clot properties were examined before and after 3-month chemotherapy mostly with cisplatin or carboplatin-based doublets. The authors hypothesized that the treatment may adversely effect of fibrin clots properties because of the well-established risk of trVTE. However, surprisingly, they reported that chemotherapy “improved” fibrin clot properties. These “improved properties” were considered to be reduced compactness and reduced fibrinolysis resistance of clots, which is generally associated with decreased

risk of trVTE (10). The clot properties that improved using chemotherapy were demonstrated by increased Ks, shortened clot lysis time, and increased fibrin porosity as shown by scanning electron microscopy.

Therefore, the study by Królczyk *et al.* was the first to demonstrate that chemotherapy improves fibrin clot properties in patients with cancer, thus providing relevant information for understanding the pathophysiology of both trVTE and non-treatment related VTE in patients with lung cancer. The unique point of the study was the evaluation of fibrin clot properties after 4 to 5 cycles of chemotherapy, which differed from previous studies that involved the evaluation of chemotherapy effects on fibrinolysis during the first or third week of the first cycle (11,12). These studies reported hypercoagulation and hypofibrinolytic activities in patients during chemotherapy, whereas the study by Królczyk *et al.* showed that repeated chemotherapy cycles finally resulted in the conversion of fibrin clots from a lysis-resistant form into a less lysis-resistant form. Moreover, they suggested molecular mechanisms for how chemotherapy improves characteristics of fibrin clots and showed that thrombin generation, which has a major impact on fibrin structure, was not affected but micro-particle (MP)-TF activity was reduced by 22% after chemotherapy. In addition, they found a weak association between MP-TF activity and Ks. Based on these findings, the authors suggested that MP-TF could directly contribute to hypofibrinolysis in patients with cancer. However, other factors that influence fibrinolysis might also be inhibited by chemotherapy, resulting in improved fibrin clot properties. Two such major factors are plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis released from tumor cells, and platelets. Future studies should focus on investigating the effects of chemotherapy on these factors and their subsequent effect on fibrin clot formation. Importantly, the authors reported an association between clot lysis time and response to chemotherapy, suggesting that chemotherapy directly contributes to the improvement of fibrin clot properties.

However, it is important to emphasize that these findings do not change the increased risk of thrombosis associated with chemotherapy. As mentioned earlier, Królczyk *et al.* focused on the late (~3 months) effects of chemotherapy on fibrin clots; however, chemotherapy-induced VTE can be encountered as early as a couple of days after drug administration. In fact, a review paper on cancer associated

VTE reported the highest incidence of VTE in the first 3 months after diagnosis of cancer (3). Information on the chemotherapeutic regimen and its time and frequency of administration is not available for this study. However, it is expected that systemic chemotherapy is performed in the first 3 months after diagnosis for most patients. Therefore, although chemotherapy may have a long-term favorable impact on fibrin clot properties after completion of several chemotherapy cycles, it may also have an unfavorable short-term impact on fibrin clot properties.

Clinically symptomatic VTE events were not reported in the study by Królczyk *et al.*, which suggests the possibility that patients having high risk for VTE were not included in their study. If this is true, the fibrin clots properties in patients having high risk for trVTE might differ from the fibrin clot properties in non-high-risk patients. In addition, in a study where patients with idiopathic VTE and their relatives were analyzed, the fibrin clots from patients who developed PE showed higher permeability, reduced compactness, and easier lysis of fibrin clots compared with the clots from patients who did not develop PE (14). This could be explained by the hypothesis that fibrin clots with such properties are more likely to fragment, leading to PE. Therefore, “improved properties” using chemotherapy might not necessarily be associated with reduced risk of VTE in patients with lung cancer. Thus, future studies should aim to include sufficient numbers of VTE events to increase statistical power. Findings from such studies would enable the identification of patients having high risk of trVTE based on fibrin clot properties.

In conclusion, Królczyk *et al.*, for the first time, reported the potentially favorable effects of 3-month chemotherapy on fibrin clot characteristics. Studies with larger sample size that also examine additional parameters for fibrin clot properties are required for further elucidation of the molecular mechanisms behind trVTE as well as for the clinical translation of the knowledge acquired from these studies.

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Footnote

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