Review

Management of Coagulopathy in Onco Critical Care unit.

Priyanka Dev, MD[1] ✉ Sunny Agarwal, MD[1]

[1.] Dept. of Anesthesia, and Critical Care, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences. Shillong, India.

Email: priyanka8ap@gmail.com

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The natural physiology of the body is maintained by a balance between various systems of the body. When a person suffers from cancer, it affects not only that particular organ but the entire functioning and wellbeing of the body is altered. In this context, we will discuss how malignancy can affect coagulation and how we can manage the resulting coagulopathies in critically ill cancer patients.

Cancer affecting coagulation may cause either bleeding or thrombosis and this depend on many factors.

Bleeding in patients with cancer may present as a localized bleeding, due to tumor invasion, or as a generalized bleeding diathesis due to thrombocytopenia, thrombocytopathies, coagulation factor deficiencies, increased fibrinolysis and anticoagulant medication. Bleeding manifestations include melena, hematuria, hematemesis, hematochezia, hemoptysis, epistaxis, vaginal bleeding or ulcerated skin lesions, ecchymoses, petechiae or bruising [1]. Cancer causes both qualitative and quantitative changes in platelets [2].

Malignancy leads to activation of coagulation cascade. In most cases it is detected through molecular markers for the factors and pathway without any clinical manifestations but when there is strong activation, it can cause thrombocytopenia and prolonged clotting time and in severe cases it can cause DIC. [3,4,5]

Trousseau's syndrome is used to indicate any type of thromboembolic manifestation occurring in cancer and includes arterial and venous thrombosis, non-bacterial thrombotic endocarditis (NBTE), thrombotic microangiopathy (TMA) and veno-occlusive disease (VOD) [1]

Thrombotic risk factors:

These risk factors may be patient related i.e., advanced age, prolong bed rest, obesity, atherosclerosis, previous thrombosis, prothrombotic mutation, SIR, sepsis etc. It may be cancer related i.e., site of cancer for example brain, pancreas, stomach, bladder, mucin secreting adenocarcinoma etc. It may be also treatment related i.e., hospitalization & surgery, chemotherapy or anti-neoplastic treatment, anti-angiogenic therapy & erythropoiesis stimulating agents, indwelling catheters and blood transfusions.

Tumor cells express tissue factor (TF) either on its surface, tumor stroma (macrophages, fibroblasts and tumor vascular endothelium) and microparticles surface[8] and thereby triggering the coagulation pathway and finally forming fibrin. Enhanced cancer cell TF expression also leads to increased tumor growth.

Tumor cell by expression of selectin ligands can also lead to clot formation. P-selectin binds to platelets and causes platelet aggregation whereas E-selectin attaches to the endothelial cell.[9]

Microparticles (MP) are 0.1–1μm diameter vesicles containing phosphatidylserine, and have been actively shed from cells. [10] During the initiation of blood coagulation, MP expressing TF and P-selectin glycoprotein ligand-1 (PSGL-1) accumulate in the platelet thrombus.[11] This phosphatidylserine and TF act together to trigger coagulation and a strong

procoagulant environment is created.[12] The expression of these procoagulant molecules and microparticles leads to the development of inappropriate coagulation in cancer.

It is found that venous thromboembolism (VTE) risk is increased to four-fold in cancer and patients on chemotherapy have a further increase to six- and seven-fold.[8] Incidence of VTE is reflected by expression of higher levels of TF in brain and pancreatic cancer and lower levels are seen in breast cancer. [13]

Chemotherapy especially in bone marrow transplant patients causes reduction in anticoagulant proteins which is thereby responsible for the thrombotic complications. Chemotherapeutic agents like mitomycin, thalidomide, gemcitabine, immunotoxins, monoclonal antibodies and tyrosine kinase inhibitors have been found to cause thrombotic microangiopathy. High-dose conventional chemotherapy that is used as conditioning regimen before autologous or allogeneic stem cell transplantation and newer biological anti-cancer agents may cause this complication.[5]

Management of bleeding complications in cancer patients

A. Thrombocytopenia

Often the treatment of bleeding associated with thrombocytopenia in the critically ill patient with cancer is managed without determining a specifically defined cause.[2] In non-bleeding patient, 10000 patient count is often the trigger for platelet transfusion.

B. Thrombocytopathies

1. Acquired von Willebrand's Syndrome: Malignancy like plasma cell dyscrasias, myeloproliferative disorders, leukemia, lymphomas, and solid tumors such as nephroblastoma, gastric carcinoma, and cancer of the adrenal gland have been found to be associated with this syndrome.[14]

2. Acquired Hemophilia (Factor VIII Autoantibodies): Factor VIII inhibitors are detected infrequently in patients who do not have hemophilia; however, patients with solid tumors, paraproteinemia's, and lymphoproliferative disorders may develop a bleeding diathesis as a consequence of an acquired hemophilia state.[15] The inhibitors are autoantibodies and almost always IgG molecules.

3. Uremia: In patients with cancer with chronic renal failure, qualitative platelet dysfunction is common and causes significant bleeding. Treatment is recommended for patients with active bleeding or for those requiring biopsy or surgery.

C. Coagulation Factor Deficiencies

Vitamin K deficiency in malignancy can occur as a consequence of malnutrition, liver disease, biliary obstruction, use of oral anticoagulants, or antibiotic therapy. These patients have increased levels of fibrinogen, unlike patients with cirrhosis or acute liver failure who have decreased fibrinogen levels.

Acquired inhibitors of coagulation factors frequently are seen in multiple myeloma and other dysproteinemias.

D. Bleeding due to anticoagulants

Management[16]

<table>
<tr><td colspan="3">Treat the underlying malignancy</td></tr>
<tr><td colspan="2">Thrombocytopenia</td><td>Platelet Transfusion</td></tr>
<tr><td rowspan="3">Thrombocytopathies</td><td>Acquired von Willebrand's Syndrome</td><td>• Desmopressin acetate (DDAVP) 0.3 µ/kg IV
• vWF concentrate 40-60U/kg IV
• Intravenous Immuneglobulin 1g/kg.</td></tr>
<tr><td>Acquired Hemophilia (Factor VIII Autoantibodies)</td><td>• Plasmapheresis
• Prednisolone 1mg/kg/day
• Cyclophosphamide 1.5-2 mg/kg/day orally
• Factor VIII concentrates.</td></tr>
<tr><td>Uremia</td><td>• Hemodialysis
• Desmopressin acetate (DDAVP) 0.3 µ/kg IV [5]</td></tr>
<tr><td colspan="2">Coagulation Factor Deficiencies</td><td>• Vitamin K: 5-10 mg oral or IV for rapid correction
• Plasma: 10-15 ml/kg IV
• Cryoprecipitate: 1unit every 5 kg of body weight</td></tr>
<tr><td colspan="2">Bleeding due to anticoagulants</td><td>• Stop the Anticoagulant - first step
• Manual compression- for skin-bleeds and epistaxis.
• Transfusion of blood products -for more significant bleeding</td></tr>
</table>

	• Reversal of anticoagulant- decision should be made based on the location of bleeding, time since last use of the anticoagulant, and patient's hemodynamic stability.

Management of Thrombotic complications in cancer patients

Thrombotic manifestations in critically ill patients with cancer may present as deep venous thrombosis (DVT), pulmonary embolism (PE), TTP/HUS, arterial thrombosis, or DIC.

Venous thrombosis is associated with significant morbidity and mortality [17] and is one of the leading causes of death in cancer. Most guidelines recommend monotherapy anticoagulation[18]

- Low-molecular-weight heparin (LMWH): 1mg/kg SC BD for 3–6 months.
- DOACs (apixaban, rivaroxaban or edoxaban) can be used for acute cancer associated VTE with low bleeding risk.

For recurrent venous thromboembolism (VTE) in cancer patients

(a)Acute phase (< 3 months) : Therapeutic dose of LMWH, thrombolysis or pharmacomechanic clot removal should be performed when recurrence causes massive VTE.

(b) Intermediate phase (3–6 months): continue same LMWH dose as in acute phase for the fourth month and after that, dose could be reduced by 25%.

(c) Long-term phase (> 6 months): LMWH (at the same dose as the intermediate phase) or DOAC or VKA should be used as long as cancer is active.

In cancer associated thrombosis (CAT) patients with absolute contraindication to anticoagulation, IVC filter should be inserted for acute (< 1 month from index VTE) or subacute CAT (1– 3 months) but not for chronic CAT (> 3 months)

Arterial thrombosis most commonly arises from embolism of sterile thrombotic vegetations from cardiac valves (nonbacterial endocarditis) adenocarcinomas of the lung and pancreas.[16] Management is similar as patients with venous thromboembolism.

In cancer patients with DIC with thrombotic complications, intravenous heparin 15 U/kg/hr without a loading dose may be used for stabilization while the cancer is being treated unless moderate to severe thrombocytopenia is present.[17]

Heparin-induced Thrombocytopenia develops in 1% to 5% of patients receiving heparin.[21] The decrease in platelet count typically occurs after 5 to 12 days of exposure to heparin but may develop sooner if there has been prior exposure to heparin during the last 3 months. Management consists of discontinuing all forms of heparin and switching to direct-acting oral anticoagulants (DOAC) for thromboprophylaxis.

Conflict of interest: Nil

References

1. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. J Thromb Haemost. 2013;11:223-33.
2. Johnson MJ: Bleeding, clotting and cancer. Clin Oncol (R Coll Radiol) 9:294, 1997
3. Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood. 2018;131:845–54.
4. Levi M, Seligsohn U. Disseminated intravascular coagulation. Williams Hematology. 10th ed.
5. Levi M. Pathophysiology of Coagulopathy in Hematological Malignancies and in COVID-19. Hemasphere 2021 5:6.
6. Levi M, Sivapalaratnam S. An overview of thrombotic complications of old and new anticancer drugs. Thromb Res. 2020;191:S17–S21
7. Levi M. Disseminated intravascular coagulation in cancer: an update. Semin Thromb Hemost. 2019;45:342–347.
8. Callander N.S., Varki N. Rao. Immunohistochemical identification of tissue factor in solid tumors. Cancer1992; 70:1194–01.
9. Laubli, H. & Borsig, L. Selectins as mediators of lung metastasis. Cancer Microenvironment2011; 3: 97–5.
10. Falanga A, Tartari C.J, Marchetti M. Microparticles in tumor progression. Thrombosis Research2012;129;S132–S136.
11. Falati S, Liu Q, Gross P. Accumulation of tissue factor into developing thrombi in vivo is dependent upon

microparticle P-selectin glycoprotein ligand 1 and platelet P-selectin. J Exp Med 2003;197:1585-98

12. Key N.S, Mackman N. Tissue factor and its measurement in whole blood, plasma, and microparticles. Seminars in Thrombosis and Hemostasis2010; 36:865–75.
13. Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. Journal of Clinical Oncology2009;27: 4834–38.
14. Veyradier A, Jenkins CS, Fressinaud E, et al: Acquired von Willebrand syndrome:From pathophysiology to management. Thromb Haemost84;175:2000
15. Hauser I, Lechner K Solid tumors and factor VIII antibodies. Thromb Haemost 82;1005:1999
16. Hirsh J, Dalen JE, Anderson DR, et al: Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest1998; 114445S.
17. Gussoni G, Frasson S, La Regina M, Di Micco P, Monreal M. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. Thromb Res.2013;131:24–30.
18. Lee AYY. Overview of VTE treatment in cancer according to clinical guidelines. Thromb Res. 2018;164:S162–7.
19. Schulman S. How I. Treat How I treat recurrent venous thrombembolism in patients receiving anticoagulant therapy. Blood 2017;129:3285–94.
20. Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY. Management of challenging cases of patients with cancer associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. J Thromb Haemost. 2013;11:1760–65.
21. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;16:1891–4.
22. Gordon LI, Kwaan HC: Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 34:140, 1997