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Cancer-associated Venous Thromboembolism and Thrombocytopenia

ABSTRACT

KEY WORDS: cancer-associated thromboembolism, thrombocytopenia, venous thromboembolism, anticoagulation therapy

Venous thromboembolism often occurs in patients with cancer. The risk of venous thromboembolism is increased because of the prothrombotic state (platelet activation, increased tissue factor expression) as well as cancer treatment (surgery, central venous lines, chemotherapy). On the other hand, thrombocytopenia also frequently develops in cancer patients due to cancer itself (e.g., in haematological malignancies) or due to anti-cancer therapy. The management of cancer-associated thromboembolism in patients with thrombocytopenia is therefore challenging due to increased risk of recurrent venous thromboembolism on one hand and increased risk of bleeding on the other. Generally, the use of full-dose anticoagulation is considered safe in patients with a platelet count above 50×10^9/L. However, in patients with more pronounced thrombocytopenia, a careful assessment of venous thromboembolism recurrence risk and risk of bleeding must be made. In this paper, we review the current recommendations regarding thrombocytopenia and cancer-associated thromboembolism management in these patients.

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CANCER AND VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients. It is estimated that approximately 15% of cancer patients will develop VTE during the course of their disease and that active cancer is responsible for up to 20% of otherwise unexplained VTE *(1, 2)*. According to recent data, the risk of VTE in cancer patients is 15-times higher than in patients without cancer *(3)*. Patients with cancer who develop VTE have a worse prognosis than those without VTE. The mechanisms of cancer-associated thromboembolism (CAT) include all the components of the Virchow triad (vessel wall damage, stasis, hypercoagulability). Many of them are cancer specific: thrombocytosis with platelet activation, leucocytosis and neutrophil extracellular traps, the expression of tissue factor and elevated levels of plasminogen activator inhibitor-1 (PAI-1). Other factors also influence the risk of CAT, i.e. cancer surgery, the insertion of central venous catheters, and chemotherapy. Because CAT recurrence rate is high and associated with poor prognosis, CAT management is challenging *(4, 5)*.

The Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial in 2003 clearly showed that treatment with low-molecular-weight heparins (LMWH) in the first six months after CAT was more effective than warfarin and this approach has long represented the mainstay of anticoagulation in CAT *(6)*. However, in recent years, several trials proved the effectiveness of direct oral anticoagulants (DOACs) for the treatment of CAT, and DOACs (rivaroxaban, apixaban, edoxaban) are now recommended as the first line anticoagulant treatment option in CAT as well *(7, 8)*. An increased risk of bleeding in gastrointestinal tumours and possible interactions with cancer treatment must be taken into account.

CANCER AND THROMBOCYTOPENIA

Thrombocytopenia often occurs in cancer patients. It can be a result of the underlying disease (e.g., in haematological malignancies), but most often it is a consequence of oncological treatment. Severe thrombocytopenia occurs in about 30% of patients with solid tumours and in about 50% of patients with haematological malignancies *(8)*. Without anticoagulant treatment, the risk of bleeding increases at a platelet count $< 25 \times 10^9$/L and the risk of spontaneous major bleeding increases at a platelet count $< 10 \times 10^9$/L. Chemotherapy-induced thrombocytopenia (CIT) is usually managed with platelet transfusions although the duration of platelet count improvement is short-lived and transfusions are not practical for the long-term maintenance of platelet count throughout chemotherapy. Therefore, platelet transfusions are usually only used in severe thrombocytopenia (platelet count $< 10 \times 10^9$/L) and/or in case of bleeding complications *(8)*. Thrombopoietin receptor agonists (TPO-RAs) are a promising therapeutic option in patients with solid tumours but are currently only approved for the treatment of specific types of thrombocytopenia (e.g. immune thrombocytopenia) and have not been tested in CIT. Due to a lack of phase 3 clinical trials, the current guidelines of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), suggest the use of TPO-RAs only in the setting of clinical trials or the use of romiplostim when considering TPO-RA use outside of clinical trial settings *(8)*.

THE MANAGEMENT OF CANCER-ASSOCIATED THROMBOEMBOLISM IN PATIENTS WITH THROMBOCYTOPENIA

CAT is associated with an increased risk of recurrence but the use of full-dose anticoagulation in thrombocytopenic patients is considered risky due to an increased risk of bleeding. Generally, the use of full-dose anticoagulation is considered safe in patients with a platelet count > 50×10^9/L *(9)*. The management of anticoagulation in patients with more pronounced thrombocytopenia is uncertain. Usually, LMWHs are used due to the lack of data on the use of DOACs in this setting. For patients with severe thrombocytopenia and acute CAT (up to one month), the guidelines suggest either a full-dose of LMWH and platelets transfusions to maintain a platelet count of 40–50×10^9/L in patients with a high risk of thrombosis progression or a 50% reduction of the LMWH dose in patients with low risk of thrombosis progression. For subacute CAT (more than one month), the guidelines suggest a 50% reduction of the LMWH dose or the use of a prophylactic LMWH dose. In patients with a platelet count < 25×10^9/L, temporary discontinuation of anticoagulation is suggested *(9)*. Some recommendations use a somewhat higher cut-off value for the discontinuation of anticoagulation at 30×10^9/L *(10)*.

CONCLUSION

CAT management is especially challenging in cancer patients with thrombocytopenia. The cause and the degree of thrombocytopenia, risk of bleeding, risk of recurrent VTE and other patient characteristics must be taken into account when selecting optimal anticoagulant treatment for such patients.

REFERENCES

1. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers. 2022; 8 (1): 11. doi: 10.1038/s41572-022-00336-y
2. Laporte S, Mismetti P, Décousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: Findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation. 2008; 117 (13): 1711–6. doi: 10.1161/CIRCULATIONAHA.107.726232
3. Grilz E, Posch F, Nopp S, et al. Relative risk of arterial and venous thromboembolism in persons with cancer vs. persons without cancer – A nationwide analysis. Eur Heart J. 2021; 42 (23): 2299–307. doi: 10.1093/eurheartj/ehab171
4. Fernandes CJ, Morinaga LTK, Alves JL, et al. Cancer-associated thrombosis: The when, how and why. Eur Respir Rev. 2019; 28 (151): 180119. doi: 10.1183/16000617.0119-2018
5. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003; 349 (2): 146–53. doi: 10.1056/NEJMoa025313
6. Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: A systematic review and meta-analysis. Blood. 2020; 136 (12): 1433-41. doi: 10.1182/blood.2020005819
7. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. Ann Oncol. 2023; 34 (5): 452–67. doi: 10.1016/j.annonc.2022.12.014
8. Soff G, Leader A, Al-Samkari H, et al. Management of chemotherapy-induced thrombocytopenia: Guidance from the ISTH Subcommittee on Hemostasis and Malignancy. J Thromb Haemost. 2024; 22 (1): 53–60. doi: 10.1016/j.jtha.2023.09.031
9. Samuelson Bannow BT, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: Guidance from the SSC of the ISTH. J Thromb Haemost. 2018; 16 (6): 1246–9. doi: 10.1111/jth.14015
10. Napolitano M, Saccullo G, Marietta M, et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: An expert consensus. Blood Transfus. 2019; 17 (3): 171-80. doi: 10.2450/2018.0143-18