

# MALIGNITE YA DA ONKOLOJİK TEDAVİ İLİŞKİLİ TROMBOTİK HASTALIKLAR

7.

## BÖLÜM

Timuçin SABUNCU<sup>1</sup>

### GİRİŞ

Trombozun, kanser hastalarında yaygın bir komplikasyon olduğunu gösteren çok sayıda çalışma vardır. Kanser hastalarında trombotik komplikasyonlar arterial veya venöz tromboembolizmden dissemine intravasküler koagülasyona kadar geniş bir yelpazede görülebilmektedir (1). Kanser ile tromboembolik hastalıklar arasındaki ilişki çok iyi bilinmesine rağmen, mekanizmaları net olarak bilinmemekte ve çok yönlü olduğu düşünülmektedir (2). Kanser hastaları genellikle hiperkoagülasyona yatkın veya protrombotik durumdadırlar ve genellikle Virchow triadının (venöz staz, endotel hasarı, hiperkoagülabilité) her bir komponentinde anormallikler göstermektedirler. Virchow triadında bu değişiklikleri meydana getiren özellikle hastanın hemostatik sisteminin etkisi tam olarak anlaşılamamıştır ve farklı kanser tiplerinde kanser bağlantılı tromboz riskinin değişen oranlarda olduğu göz önünde bulundurulduğunda tümör-spesifik olabilir (3).

### KANSERDE HEMOSTAZ DEĞİŞİMLERİNE NEDEN OLAN MOLEKÜL VE MEKANİZMALAR

*Doku Faktörü ve Doku Faktörü Taşıyan Mikropartikiiller:* Kanser hastalarındaki prokoagulan aktivitede en önemli faktörlerden biridir. Faktör VII ile birleşerek ekstrensek yolak ile koagülasyonu aktive eder (4, 5). Doku Faktörü taşıyan mikropartiküllerin venöz tromboembolizmi(VTE) bulunan kanser hastalarının %60'ında yüksek olduğu gösterilmiştir (5, 6).

*Kanser Prokoagülanı:* Amniyotik doku ve malign tümörler tarafından eksprese edilen bir sistein proteazdır (5).

*Müsür:* GIS tümörleri, müsin üreterek Faktör X'u aktive eder ve koagülasyona yol açar. (kilavuzu öne al)

<sup>1</sup> Uzm. Dr., Timuçin Sabuncu Hacettepe Üniversitesi Kalp Damar Cerrahisi  
ORCID iD: 0000-0002-1943-949X

## REFERANSLAR

- Levi M. Cancer-related coagulopathies. *Thromb Res.* 2014;133 Suppl 2:S70-S75. doi:10.1016/S0049-3848(14)50012-6
- Falanga A, Marchetti M, Russo L. The mechanisms of cancer-associated thrombosis. *Thromb Res.* 2015;135 Suppl 1:S8-S11. doi:10.1016/S0049-3848(15)50432-5
- Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-Associated Thrombosis: An Overview of Mechanisms, Risk Factors, and Treatment. *Cancers (Basel).* 2018;10(10):380. Published 2018 Oct 11. doi:10.3390/cancers10100380
- Demir AM, Ümit EG. Kanserle İlişkili Tromboz. *Türkiye Klinikleri J Hematol-Special Topics.* 2015;8(3):66-74
- Khalil J, Bensaid B, Elkacemi H, et al. Venous thromboembolism in cancer patients: an underestimated major health problem. *World J Surg Oncol.* 2015;13:204. Published 2015 Jun 20. doi:10.1186/s12957-015-0592-8
- Zwicker JI, Liebman HA, Neuberg D, et al. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. *Clin Cancer Res.* 2009;15(22):6830-6840. doi:10.1158/1078-0432.CCR-09-0371
- GüVen Platformu. Ulusal Venöz Tromboembolizm Profilaksi ve Tedavi Kılavuzu-2016. Ed: Demir M., Öngen G., Tural D. cortex iletişim 2016
- Falanga A, Russo L, Milesi V. The coagulopathy of cancer. *Curr Opin Hematol.* 2014;21(5):423-429. doi:10.1097/MOH.0000000000000072
- Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost.* 2013;11(2):223-233. doi:10.1111/jth.12075
- Falanga A, Panova-Noeva M, Russo L. Procoagulant mechanisms in tumour cells. *Best Pract Res Clin Haematol.* 2009;22(1):49-60. doi:10.1016/j.beha.2008.12.009
- Nadir Y, Brenner B, Gingis-Velitski S, et al. Heparanase induces tissue factor pathway inhibitor expression and extracellular accumulation in endothelial and tumor cells. *Thromb Haemost.* 2008;99(1):133-141.
- Demers M, Wagner DD. Neutrophil extracellular traps: A new link to cancer-associated thrombosis and potential implications for tumor progression. *Oncoimmunology.* 2013;2(2):e22946. doi:10.4161/onci.22946
- Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. *Arterioscler Thromb Vasc Biol.* 2012;32(8):1777-1783. doi:10.1161/ATVBA-HA.111.242859
- Aird WC. Vascular bed-specific thrombosis. *J Thromb Haemost.* 2007;5 Suppl 1:283-291. doi:10.1111/j.1538-7836.2007.02515.x
- Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerström J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost.* 2007;5(4):692-699. doi:10.1111/j.1538-7836.2007.02450.x
- Connolly GC, Francis CW. Cancer-associated thrombosis. *Hematology Am Soc Hematol Educ Program.* 2013;2013:684-691. doi:10.1182/asheducation-2013.1.684
- Agnelli G, Verso M. Management of venous thromboembolism in patients with cancer. *J Thromb Haemost.* 2011;9 Suppl 1:316-324. doi:10.1111/j.1538-7836.2011.04346.x
- Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-722. doi:10.1001/jama.293.6.715
- Sud R, Khorana AA. Cancer-associated thrombosis: risk factors, candidate biomarkers and a risk model. *Thromb Res.* 2009;123 Suppl 4:S18-S21. doi:10.1016/S0049-3848(09)70137-9
- Navi BB, Reiner AS, Kamel H, et al. Risk of Arterial Thromboembolism in Patients With Cancer. *J Am Coll Cardiol.* 2017;70(8):926-938. doi:10.1016/j.jacc.2017.06.047
- Tuzovic M, Herrmann J, Iliescu C, Marmagkiolis K, Ziaeian B, Yang EH. Arterial Thrombosis in Patients with Cancer. *Curr Treat Options Cardiovasc Med.* 2018;20(5):40. Published 2018 Apr 7. doi:10.1007/s11936-018-0635-x

22. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: A PRISMA-compliant systemic review and meta-analysis. *Medicine (Baltimore)*. 2016;95(32):e4495. doi:10.1097/MD.00000000000004495
23. Levi M. Management of cancer-associated disseminated intravascular coagulation. *Thromb Res.* 2016;140 Suppl 1:S66-S70. doi:10.1016/S0049-3848(16)30101-3
24. Kwaan HC, Gordon LI. Thrombotic microangiopathy in the cancer patient. *Acta Haematol.* 2001;106(1-2):52-56. doi:10.1159/000046589
25. Pi J, Kang Y, Smith M, Earl M, Norigian Z, McBride A. A review in the treatment of oncologic emergencies. *J Oncol Pharm Pract.* 2016;22(4):625-638. doi:10.1177/1078155215605661
26. Lee, K.; Hwang,I.G.; Jang, J.; Park, S.H.; Kang J.H.; Oh, S.Y.; Kwon, H.; Lim, D.H.; Park, K.; Lee, S. Treatment outcomes of chemotherapy for advanced gastric cancer with disseminated intravascular coagulation. *J. Clin. Oncol.* 2011, 29, e14532
27. Wada H, Matsumoto T, Suzuki K, et al. Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy. *Thromb J.* 2018;16:14. Published 2018 Jul 11. doi:10.1186/s12959-018-0168-2
28. Sallah S, Wan JY, Nguyen NP, Hanrahan LR, Sigounas G. Disseminated intravascular coagulation in solid tumors: clinical and pathologic study. *Thromb Haemost.* 2001;86(3):828-833.
29. Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. *Semin Thromb Hemost.* 2001;27(6):593-604. doi:10.1055/s-2001-18865
30. Pasquini E, Gianni L, Aitini E, et al. Acute disseminated intravascular coagulation syndrome in cancer patients. *Oncology.* 1995;52(6):505-508. doi:10.1159/000227520
31. Ojeda-Uribe M, Merieau S, Guillon M, et al. Secondary thrombotic microangiopathy in two patients with Philadelphia-positive hematological malignancies treated with imatinib mesylate. *J Oncol Pharm Pract.* 2016;22(2):361-370. doi:10.1177/1078155214568580
32. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158(6):585-593. doi:10.1001/archinte.158.6.585
33. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer.* 2007;110(10):2339-2346. doi:10.1002/cncr.23062
34. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol.* 2006;24(3):484-490. doi:10.1200/JCO.2005.03.8877
35. Levy-Mendelovich S, Barg AA, Kenet G. Thrombosis in pediatric patients with leukemia. *Thromb Res.* 2018;164 Suppl 1:S94-S97. doi:10.1016/j.thromres.2018.01.019
36. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med.* 2006;166(4):458-464. doi:10.1001/archinte.166.4.458
37. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol.* 2007;44(2):62-69. doi:10.1053/j.seminhematol.2007.02.004
38. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol.* 2009;27(29):4839-4847. doi:10.1200/JCO.2009.22.3271
39. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med.* 2012;9(7):e1001275. doi:10.1371/journal.pmed.1001275
40. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. *Thromb Res.* 2006;118(5):555-568. doi:10.1016/j.thromres.2005.10.015
41. Ahlbrecht J, Dickmann B, Ay C, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol.* 2012;30(31):3870-3875. doi:10.1200/JCO.2011.40.1810
42. Fuentes HE, Tafur AJ, Caprini JA. Cancer-associated thrombosis. *Dis Mon.* 2016;62(5):121-158. doi:10.1016/j.dismonth.2016.03.003

43. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. *Ann Surg.* 2006;243(1):89-95. doi:10.1097/01.sla.0000193959.44677.48
44. Piovella F, Wang CJ, Lu H, et al. Deep-vein thrombosis rates after major orthopedic surgery in Asia. An epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. *J Thromb Haemost.* 2005;3(12):2664-2670. doi:10.1111/j.1538-7836.2005.01621.x
45. Nathan SS, Simmons KA, Lin PP, et al. Proximal deep vein thrombosis after hip replacement for oncologic indications. *J Bone Joint Surg Am.* 2006;88(5):1066-1070. doi:10.2106/JBJS.D.02926
46. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer.* 2013;119(3):648-655. doi:10.1002/cncr.27772
47. Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. *Ann Intern Med.* 1986;105(1):48-51. doi:10.7326/0003-4819-105-1-48
48. Numico G, Garrone O, Dongiovanni V, et al. Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. *Cancer.* 2005;103(5):994-999. doi:10.1002/cncr.20893
49. Czajkowski PM, Moore MJ, Tannock IF. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. *J Urol.* 1998;160(6 Pt 1):2021-2024. doi:10.1097/00005392-199812010-00022
50. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol.* 2015;12(8):464-474. doi:10.1038/nrcardio.2015.83
51. Sugiyama K, Narita Y, Kadokawa S, Ura T, Tajika M, Muro K. Platinum-based Doublet Chemotherapy for Advanced Gastric Cancer with Disseminated Intravascular Coagulation. *Anticancer Res.* 2017;37(1):309-313. doi:10.21873/anticanres.11322
52. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA.* 2008;300(19):2277-2285. doi:10.1001/jama.2008.656
53. Schutz FA, Je Y, Azzi GR, Nguyen PL, Choueiri TK. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. *Ann Oncol.* 2011;22(6):1404-1412. doi:10.1093/annonc/mdq587
54. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab [published correction appears in *J Natl Cancer Inst.* 2008 Jan 16;100(2):156] [published correction appears in *J Natl Cancer Inst.* 2008 May 7;100(9):685]. *J Natl Cancer Inst.* 2007;99(16):1232-1239. doi:10.1093/jnci/djm086
55. Lee AY, Levine MN, Butler G, et al. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. *J Clin Oncol.* 2006;24(9):1404-1408. doi:10.1200/JCO.2005.03.5600
56. Pinelli F, Balsorano P. Catheter-related thrombosis natural history in adult patients: a tale of controversies, misconceptions, and fears. *J Vasc Access.* 2020;21(4):405-407. doi:10.1177/1129729819879818
57. Balestreri L, De Cicco M, Matovic M, Coran E, Morassut S. Central venous catheter-related thrombosis in clinically asymptomatic oncologic patients: a phlebographic study. *Eur J Radiol.* 1995;20(2):108-111. doi:10.1016/0720-048x(95)00633-2
58. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol.* 2019;20(10):e566-e581. doi:10.1016/S1470-2045(19)30336-5.
59. Lee AY, Peterson EA. Treatment of cancer-associated thrombosis. *Blood.* 2013;122(14):2310-2317. doi:10.1182/blood-2013-04-460162

60. Wang TF, Li A, Garcia D. Managing thrombosis in cancer patients. *Res Pract Thromb Haemost.* 2018;2(3):429-438. Published 2018 May 1. doi:10.1002/rth2.12102
61. 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):146-153. doi:10.1056/NEJMoa025313
62. Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial [published correction appears in JAMA. 2017 Nov 28;318(20):2048]. *JAMA.* 2015;314(7):677-686. doi:10.1001/jama.2015.9243
63. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med.* 2018;378(7):615-624. doi:10.1056/NEJMoa1711948
64. Hernandez C, Huebener P, Schwabe RF. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene.* 2016;35(46):5931-5941. doi:10.1038/onc.2016.104