



ONKOLOJİ HASTALARINDA DERİN VEN TROMBOZU YÖNETİMİ

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GİRİŞ

Venöz tromboembolizm (VTE) sık görülmesi, tekrarlama riskinin yüksek olması, yaşam kalitesi ve sağkalım süresini kısaltması yanında yüksek maliyetlere yol açmasıyla önemli bir halk sağlığı sorun olarak kabul edilmektedir. Genel nüfusta VTE'nin ortalama yıllık insidans oranı 100.000'de 104-183 aralığındadır ve inme insidansına benzerdir (1).VTE riskine göre görülme sıklığı, çalışmadan çalışmaya geçişle birlikte ortalama olarak yılda 13/1000 iken, yüksek riskli olgularda görülme sıklığı 68/1000'e kadar çıkmaktadır (2). Kanserli olgularda ise VTE gelişme riskinin, kanseri olmayanlara kıyasla 4-7 kat daha yüksek olduğu bilinmektedir (1).Kanserin en sık görülen komplikasyonlarından biri olan VTE, kansere bağlı ölüm nedenleri arasında ikinci sırada yer almaktadır (2).Son yıllarda VTE sıklığının kanserli olgularda da arttığı görülmektedir. Kanserde VTE, pek çok faktöre bağlı olarak ortaya çıkmakla birlikte, ana fizyopatolojik etmen kanser ve konak hücrelerinin etkileşimleri sonucunda oluşan hiperkoagülabilitate tablosudur (2,3).Kanserli olgularda gelişen trombotik olaylar; klinik seyri değiştirmekte, morbidite ve mortalite artışına neden olmaktadır (2).Bu nedenlerle kanser hastalarında VTE gelişiminin öngörülmesi, engellenmesi ve tedavisi en az kanserin birincil tedavisi kadar önemlidir.

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KAYNAKLAR

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:3-14.
2. Demir AM, Ümit EG. Kanserle İlişkili Tromboz. *Türkiye Klinikleri J Hematol-Special Topics*. 2015;8(3):66-74.
3. Falanga A, Russo L, Milesi V. The coagulopathy of cancer. *Curr Opin Hematol*. 2014;21(5):423-429.
4. Douma RA, Kok MG, Verberne LM, Kamphuisen PW, Büller HR. Incidental venous thromboembolism in cancer patients: prevalence and consequence. *Thromb Res*. 2010;125(6):e306-309.
5. Gary T, Belaj K, Steidl K, Pichler M, Eisner F, Stöger H, et al. Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients: impact on shortterm survival. *Br J Cancer*. 2012;107(8):1244-1248.
6. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160(6):809-815.
7. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.
8. 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.
9. 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;16 (4):458-464.
10. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med*. 2000;343(25):1846-1850.
11. Bauer KA. Risk and prevention of venous thromboembolism in adults with cancer. (<http://www.uptodate.com>) Mar 2016. Erişim tarihi: 12.4.2016.
12. Elyamany G, Alzahrani AM, Bukhary E. Cancer-associated thrombosis: an overview. *Clinical Medicine Insights: Oncology*. 2014;8:129-137.
13. Prandoni P, Falanga A, Piccioli A. Cancer, thrombosis and heparin-induced thrombocytopenia. *Thromb Res*. 2007;120 Suppl 2:S137-40.
14. Wun T, White RH. Venous thromboembolism (VTE) in patients with cancer: epidemiology and risk factors. *Cancer Invest* 2009;27 Suppl 1:63-74.
15. Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Thirwell J. Prevention of Fatal Postoperative pulmonary embolism by low doses of heparin. Reappraisal of result of international multicentre trial. *Lancet*. 1977;1(8011):567-569.
16. Merkow RP, Bilimoria KY, McCarter MD, Cohen ME, Barnett CC, Raval MV, et al. Post-discharge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis. *Ann Surg*. 2011; 254:131-137.
17. Okutan O, Ayten Ö. Venöz tromboembolizm ve kanser. *Tuberk Toraks*. 2014;62(4):301-315.

18. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. *Thrombosis Research*. 2006;118:555-568.
19. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost*. 2013;11(2):223-233.
20. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost*. 2006;4:529-535. 61
21. NICE. Venous thromboembolism: reducing the risk for patients in hospital Clinical guideline Published: 27 January 2010, Last updated June 2015. nice.org.uk/guidance/cg92.
22. Farge D, Deboudeau P, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost*. 2013;11:56-70.
23. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians. Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S-e226S.
24. Gould MK, Garcia DA, Wren SM, Karanicolas PC, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e227S-e277S.
25. Carrier M, Khorana AA, Moretto P, Le Gal G, Karp R, Zwicker JI. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. *Am J Med*. 2014;127(1):82-6.e1.
26. Di Nisio M, Carrier M, Lyman CGH, Khorana AA for the Subcommittee on Haemostasis and Malignancy. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1746-1749.
27. Kroger K, Weiland D, Ose C, Neumann N, Weiss S, Hirsch C, et al. Risk factors for venous thromboembolic events in cancer patients. *Ann Oncol*. 2006;17:297-303.
28. Deitcher SR, Gomes MP. The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. *Cancer*. 2004;101(3):439-449.
29. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99:1232-1239.
30. Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. *Acta Oncologica*. 2010;49:287-297.
31. Cavo M, Zamagni E, Cellini C, Tosi P, Cangini D, Cini M, et al. Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. *Blood*. 2002;100:2272-2273.
32. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR; Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with

- dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2006;24:431-436.
33. Osman K, Comenzo R, Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. *N Engl J Med.* 2001;344:1951-1952.
 34. Zonder JA, Barlogie B, Durie BG, McCoy J, Crowley J, Hussein MA. Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis. *Blood.* 2006;108:403.
 35. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. *N Engl J Med.* 2006;354:2079-2080.
 36. Morgan GJ, Schey SA, Wu P, Srikanth M, Phekoo KJ, Jenner M, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. *Br J Haematol.* 2007;137:268-269.
 37. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst.* 2006;98:708-714. 62
 38. Khalil J, Bensaid B, Elkacemi H, Afif M, Bensaid Y, Kebdani T, Benjaafar N. Venous thromboembolism in cancer patients: an underestimated major health problem. *World Journal of Surgical Oncology.* 2015;13:204.
 39. Casiato DA. Hematologic complications. In Casiato DA, Territo MA (eds). *Manual of Clinical Oncology.* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2004:651-653.
 40. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusion, thrombosis, and mortality in hospitalized patients with cancer. *Arch Intern Med.* 2008;168:2377-2381.
 41. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol.* 2009;27(25):4124-4129.
 42. Rickles FR, Falanga A. Activation of clotting factors in cancer. *Cancer Treat Res* 2009;148:31-41.
 43. Kansu E. Thrombosis in stem cell transplantation. *Hematology.* 2012;17(Suppl. 1): S159-S162.
 44. Coppel JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant.* 2010;16:157-168.
 45. Bauer KA. Pathogenesis of the hypercoagulable state associated with malignancy (<http://www.uptodate.com>) Apr 2016. Erişim tarihi: 11.5.2016.
 46. Thaler J, Ay C, Mackman N, Bertina RM, Kaider A, Marosi C, et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. *J Thromb Haemost.* 2012;10(7):1363-1370.
 47. Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R, et al. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. *Clin Cancer Res.* 2009;15(22):6830-6840.

48. Falanga A, Panova-Noeva M, Russo L. Procoagulant mechanisms in tumour cells. *Best Pract Res Clin Haematol.* 2009;22:49-60.
49. Nadir Y, Brenner B, Gingis-Velitski S, Levy-Adam F, Ilan N, Zcharia E, et al. Heparanase induces tissue factor pathway inhibitor expression and extracellular accumulation in endothelial and tumor cells. *Thromb Haemost.* 2008;99(1):133-141.
50. Garnier D, Magnus N, D'Asti E, Hashemi M, Meehan B, Milsom C, et al. Genetic pathways linking hemostasis and cancer. *Thromb Res.* 2012;129 Suppl 1:S22-S29.
51. Regina S, Valentin JB, Lachot S, Lemarié E, Rollin J, Gruel Y. Increased tissue factor expression is associated with reduced survival in non-small cell lung cancer and with mutations of TP53 and PTEN. *Clin Chem.* 2009;55(10):1834-1842.
52. 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.
53. NCCN Clinical Practice Guidelines in Oncology. Cancer-Associated Venous Thromboembolic Disease. Version 1.2015. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf Erişim Tarihi: 1.6.2016.
54. Sohne M, Kruijper MJ, Nijkeuter M, Tick L, Kwakkel H, Halkes SJ, et al. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. *J Thromb Haemost.* 2006May;4(5):1042-1046.
55. Kanne JP, Lalani TA. Role of computed tomography and magnetic resonance imaging for deep venous thrombosis and pulmonary embolism. *Circulation.* 2004;109[suppl I]:I-15-I-21. 63
56. Zierler BK. Ultrasonography and diagnosis of venous thromboembolism. *Circulation* 2004;109(12 Suppl1):19-14.
57. Lim KE, Hsu WC, Hsu YY, Chu PH, Ng CJ. Deep venous thrombosis: comparison of indirect multidetector CT venography and sonography of lower extremities in 26 patients. *Clin Imaging.* 2004 Nov-Dec;28(6):439-444.
58. Male C, Chait P, Ginsberg JS, Hanna K, Andrew M, Halton J, et al. Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children: results of the PARKAA study. Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase. *Thromb Haemost.* 2002;87(4):593-598.
59. Gaitini D. Current approaches and controversial issues in the diagnosis of deep vein thrombosis via duplex Doppler ultrasound. *J Clin Ultrasound.* 2006;34(6):289-297.
60. Costantini M, Bossone E, Renna R, Sticchi G, Licci E, De Fabrizio G, et al. Electrocardiographic features in critical pulmonary embolism. Results from baseline and continuous electrocardiographic monitoring. *Ital Heart J.* 2004;5(3):214-216.
61. Khorana AA. Cancer and thrombosis: implications of published guidelines for clinical practice. *Annals of Oncology.* 2009;20:1619-1630.
62. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008;111:4902-4907.

63. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. *Intern Emerg Med*. 2012;7(3):291-292.
64. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22(2):414-423.
65. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. *Circulation*. 2012;126(4):448-454.
66. den Exter PL, Kooiman J, Huisman MV. Validation of the Ottawa prognostic score for the prediction of recurrent venous thromboembolism in patients with cancer-associated thrombosis. *J Thromb Haemost*. 2013;11(5):998-1000.
67. Di Castelnuovo A, de Curtis A, Costanzo S, et al. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. *Haematologica*. 2013; 98:1476-1480.
68. Altiay G, Ciftci A, Demir M, Kocak Z, Sut N, Tabakoglu E, et al. High plasma D-dimer level is associated with decreased survival in patients with lung cancer. *Clin Oncol (R Coll Radiol)*. 2007;19(7):494-498.
69. GüVen Platformu. Ulusal Venöz Tromboembolizm Profilaksi ve Tedavi Kılavuzu – 2010. Ed: Demir M, Erdemli B, Kurtoğlu M, Öngen G. cortex iletişim 2010.
70. Cohen AT, Alikhan R, Arcelus JI, Bergmann JF, Haas S, Merli GJ, et al. Assessment of venous thromboembolism risk and the benefits of thromboprophylaxis in medical patients. *Thromb Haemost*. 2005;94:750-759.
71. Caprini JA. Venous thromboembolism risk factor assessment. www.med.umich.edu/clinical/images/VTERiskAssessment.pdf, 1.5.2007.
72. İstanbul Üniversitesi, İstanbul Tıp Fakültesi Genel Cerrahi Anabilim Dalı. DVT Profilaksisi Risk Değerlendirme Formu, 2009.
73. Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet*. 2008; 371: 387-394. 64
74. Ongen G, Yilmaz A, Cirak AK, Ersoy CY, Erden F, Altintas F, et al. Venous thromboembolism risk and thromboprophylaxis among hospitalized patients: data from the Turkish Arm of the ENDORSE Study. *Clinical and Applied Thrombosis/Hemostasis*. 2011;17(5):539-545.
75. Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double blind trial. *Haemostasis*. 1986;16:159-164.
76. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*. 1999;341:793-800.
77. McGarry LJ, Stokes ME, Thompson D. Outcomes of thromboprophylaxis with enoxaparin vs. unfractionated heparin in medical inpatients. *Thrombosis Journal*. 2006;4(17):1-9.

78. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110:874-879.
79. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomized placebo controlled trial. *BMJ*. 2006;332:325-329.
80. Perry SL, Bohlin C, Reardon DA, Desjardins A, Friedman AH, Friedman HS, Vredenburgh JJ. Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. *J Neurooncol*. 2009; 95(1): 129-134.