

## Bölüm 13

# ONKOLOJİK TEDAVİ İLİŞKİLİ TROMBOSİTOPENİ YÖNETİMİ

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### GİRİŞ

Trombositopeni kanser hastalarında sık görülen bir komplikasyondur. Oluşturduğu kanama riski nedeniyle mortalitesi ve morbitadesi yüksek bir problemdir. Sadece kanama riski oluşturmayıp tedavi kürlerinin aksamasına, tedavi dozunun azaltılmasına neden olmaktadır<sup>(1,2)</sup>. Tedavi dozunun azaltılması ile toplam sağ kalım, progresyonsuz sağ kalım ve toplam yanıt oranının azaldığı çalışmalarda gösterilmiştir<sup>(3,4)</sup>. Bunun için erken tanınması ve nedene uygun olarak iyi yönetilmesi gerekir.

Kanser hastalarında en sık trombositopeni nedenleri sitotoksik etki gösteren kemoterapi ve radyoterapidir<sup>(5-8)</sup>. Diğer sık karşılaşılan nedenler ise kemik iliğinin hastalık ilişkili infiltrasyonu, yardımcı tedavide kullanılan antibiyotik, heparin gibi kemoterapi dışı ilaçlar, enfeksiyonlar, immün olaylar, hastalık ya da ilaç ilişkili oluşan trombotik mikroanjyopatiler ve splenomegalilerdir<sup>(9,10)</sup>. Onkoloji hastasında trombositopeni saptandığında tedavi ilişkili olduğunu düşünmeden diğer nedenlerin ekarte edilmesi gerekir.

Bu konuda sadece onkolojik tedavi ilişkili trombositopeni ve bu durumun yönetiminden bahsedilecektir.

### ONKOLOJİK TEDAVİ İLİŞKİLİ TROMBOSİTOPENİ TANIMI VE NEDENLERİ

#### Trombositopeni tanımı:

Trombositopeni trombosit sayısının  $150 \times 10^9/L$  altına düşmesi olarak tanımlanır<sup>(11)</sup>. Tedavi sonrası gelişen trombositopenide ise derecelendirilme yapılır ve onkolojide kullanılan Birleşik Devletler Ulusal Kanser Enstitüsünün Yan Etki Ortak Terminoloji Kriterlerine göre derecelendirilmesi tablo 1' de gösterilmiştir<sup>(12)</sup>.

**Tablo 1: Trombositopenin Birleşik Devletler Ulusal Kanser Enstitüsünün yan etki ortak terminoloji kriterlerine göre derecelendirilmesi**

Derece	Trombositopeni sayısı
1	Normal değer alt sınırı- $75 \times 10^9/L$
2	$75-50 \times 10^9/L$
3	$50-25 \times 10^9/L$
4	$<25 \times 10^9/L$
5	Ölüm

#### Onkolojik tedavi ilişkili trombositopeni nedenleri:

**1) Kemoterapi ilişkili kemik iliği supresyonu:** Bazı antineoplastik ajanlar kemik iliğinde hipoplazi ve miyelosupresyon oluşturması sonucu trombositopeni yaparlar. Solid tümörlerde trom-

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laşması, gaitada siyahlaşma veya kan gelmesi, kesi durumunda durmayan kanamalar gibi) doktoruna ya da en yakın sağlık kuruluşuna başvurması

- 8) Tampon, fitil, lavman ya da makattan ateş ölçen termometreler kullanılmamalı
- 9) Sıkan ve sert kumaşlı kıyafetler giyilmemeli
- 10) Duş alırken ılık su ile duş alınmalı ve keselenme gibi kanam riskini artıracak hareketlerden kaçınılmalı

**Anahtar Kelimeler:** kanser, onkolojik tedavi, trombositopeni, kanama

## KAYNAKLAR

1. Mones JV and Soff G. Management of Thrombocytopenia in Cancer Patients. *Cancer treatment and research*. 2019; 179 139-150. Doi: 10.1007/978-3-030-20315-3\_9.
2. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park, N.Y.)*. 2015; 29 (4), 282-294. Doi:
3. Nakayama G, Tanaka C, Uehara K, et al. The impact of dose/time modification in irinotecan- and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. *Cancer chemotherapy and pharmacology*. 2014; 73 (4), 847-855. Doi: 10.1007/s00280-014-2416-x.
4. Denduluri N, Patt DA, Wang Y, et al. Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2015; 13 (11), 1383-1393. Doi: 10.6004/jnccn.2015.0166.
5. Smith RE. Trends in recommendations for myelosuppressive chemotherapy for the treatment of solid tumors. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2006; 4 (7), 649-658. Doi: 10.6004/jnccn.2006.0056.
6. Huang YM, Wang CH, Huang JS, et al. Treatment-associated severe thrombocytopenia affects survival rate in esophageal cancer patients undergoing concurrent chemoradiotherapy. *Indian journal of cancer*. 2015; 52 (3), 454-460. Doi: 10.4103/0019-509X.176708.
7. Kishida Y, Hirose T, Shirai T, et al. Myelosuppression induced by concurrent chemoradiotherapy as a prognostic factor for patients with locally advanced non-small cell lung cancer. *Oncol Lett*. 2011; 2 (5), 949-955. Doi: 10.3892/ol.2011.348.
8. Wu Y, Aravind S, Ranganathan G, et al. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. *Clinical therapeutics*. 2009; 31 Pt 2 2416-2432. Doi: 10.1016/j.clinthera.2009.11.020.
9. Liebman HA. Thrombocytopenia in cancer patients. *Thrombosis research*. 2014; 133 Suppl 2 S63-S69. Doi: 10.1016/S0049-3848(14)50011-4.
10. Ghanavat M, Ebrahimi M, Rafieemehr H, et al. Thrombocytopenia in solid tumors: Prognostic significance. *Oncology reviews*. 2019; 13 (1), 413-413. Doi: 10.4081/oncol.2019.413.
11. Cheng CK-W, Chan J, Cembrowski GS, et al. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. *Laboratory hematology : official publication of the International Society for Laboratory Hematology*. 2004; 10 (1), 42-53. Doi: 10.1532/lh96.04010.
12. NIH-NCI (2017). *CTCAE V5 - Common Terminology Criteria for Adverse Events Version 5.0*. (14/01/2020 tarihinde [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) adresinden ulaşılmıştır).
13. Tamamyan G, Danielyan S and Lambert MP. Chemotherapy induced thrombocytopenia in pediatric oncology. *Critical reviews in oncology/hematology*. 2016; 99 299-307. Doi: 10.1016/j.critrevonc.2016.01.005.
14. Dy GK and Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: a cancer journal for clinicians*. 2013; 63 (4), 249-279. Doi: 10.3322/caac.21184.
15. Lonial S, Waller EK, Richardson PG, et al. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. *Blood*. 2005; 106 (12), 3777-3784. Doi: 10.1182/blood-2005-03-1173.
16. Bakchoul T and Marini I. Drug-associated thrombocytopenia. *Hematology. American Society of Hematology. Education Program*. 2018; 2018 (1), 576-583. Doi: 10.1182/asheducation-2018.1.576.
17. Cuker A, Coles AJ, Sullivan H, et al. A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. *Blood*. 2011; 118 (24), 6299-6305. Doi: 10.1182/blood-2011-08-371138.
18. Hegde UP, Wilson WH, White T, et al. Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. *Blood*. 2002; 100 (6), 2260-2262. Doi:
19. Shiuan E, Beckermann KE, Ozgun A, et al. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. *Journal for immunotherapy of cancer*. 2017; 5 8-8. Doi: 10.1186/s40425-017-0210-0.
20. Aster RH, Curtis BR, McFarland JG, et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *Journal of thrombosis and haemostasis : JTH*. 2009; 7 (6), 911-918. Doi: 10.1111/j.1538-7836.2009.03360.x.
21. George JN and Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014; 371 (7), 654-666. Doi: 10.1056/NEJMra1312353.
22. Al-Nouri ZL, Reese JA, Terrell DR, et al. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood*. 2015; 125 (4), 616-618. Doi: 10.1182/blood-2014-11-611335.
23. Gerber DE, Grossman SA, Zeltzman M, et al. The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. *Neuro-oncology*. 2007; 9 (1), 47-52. Doi: 10.1215/15228517-2006-024.

24. Lovecchio F. Heparin-induced thrombocytopenia. *Clinical toxicology (Philadelphia, Pa.)*. 2014; 52 (6), 579-583. Doi: 10.3109/15563650.2014.917181.
25. Warkentin TE and Greinacher A. Management of heparin-induced thrombocytopenia. *Current opinion in hematology*. 2016; 23 (5), 462-470. Doi: 10.1097/MOH.0000000000000273.
26. Obeng EA, Harney KM, Moniz T, et al. Pediatric heparin-induced thrombocytopenia: prevalence, thrombotic risk, and application of the 4Ts scoring system. *The Journal of pediatrics*. 2015; 166 (1), 144-150. Doi: 10.1016/j.jpeds.2014.09.017.
27. Lee E-J and Lee AI. Thrombocytopenia. *Primary care*. 2016; 43 (4), 543-557. Doi: 10.1016/j.pop.2016.07.008.
28. Khorana AA, Carrier M, Garcia DA, et al. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. *Journal of thrombosis and thrombolysis*. 2016; 41 (1), 81-91. Doi: 10.1007/s11239-015-1313-4.
29. Terpos E, Kleber M, Engelhardt M, et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica*. 2015; 100 (10), 1254-1266. Doi: 10.3324/haematol.2014.117176.
30. Choueiri TK, Schutz FAB, Je Y, et al. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010; 28 (13), 2280-2285. Doi: 10.1200/JCO.2009.27.2757.
31. Horsted F, West J and Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS medicine*. 2012; 9 (7), e1001275-e1001275. Doi: 10.1371/journal.pmed.1001275.
32. Chee CE, Ashrani AA, Marks RS, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood*. 2014; 123 (25), 3972-3978. Doi: 10.1182/blood-2014-01-549733.
33. Trujillo-Santos J, Ruiz-Gamietea A, Luque JM, et al. Predicting recurrences or major bleeding in women with cancer and venous thromboembolism. Findings from the RIETE Registry. *Thrombosis research*. 2009; 123 Suppl 2 S10-S15. Doi: 10.1016/S0049-3848(09)70003-9.
34. Papakotoulas P, Tsoukalas N, Christopoulou A, et al. Management of Cancer-associated Thrombosis (CAT): Symptomatic or Incidental. *Anticancer research*. 2020; 40 (1), 305-313. Doi: 10.21873/anticancer.13954.
35. Webert K, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. *Haematologica*. 2006; 91 (11), 1530-1537. Doi: 10.1016/j.haematologica.2006.09.011.
36. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Annals of internal medicine*. 2015; 162 (3), 205-213. Doi: 10.7326/M14-1589.
37. Schiffer CA, Bohlke K, Delaney M, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018; 36 (3), 283-299. Doi: 10.1200/JCO.2017.76.1734.
38. Fletcher CH, DomBourian MG and Millward PA. Platelet transfusion for patients with cancer. *Cancer control : journal of the Moffitt Cancer Center*. 2015; 22 (1), 47-51. Doi: 10.1177/107327481502200107.
39. Benjamin RJ and Anderson KC. What is the proper threshold for platelet transfusion in patients with chemotherapy-induced thrombocytopenia? *Critical reviews in oncology/hematology*. 2002; 42 (2), 163-171. Doi: 10.1016/s1040-8428(01)00182-2.
40. Humbrecht C, Kientz D and Gachet C. Platelet transfusion: Current challenges. *Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine*. 2018; 25 (3), 151-164. Doi: 10.1016/j.tracli.2018.06.004.
41. Singh S, Shams Hakimi C, Jeppsson A, et al. Platelet storage lesion in interim platelet unit concentrates: A comparison with buffy-coat and apheresis concentrates. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2017; 56 (6), 870-874. Doi: 10.1016/j.transci.2017.10.004.
42. Schrezenmeier H and Seifried E. Buffy-coat-derived pooled platelet concentrates and apheresis platelet concentrates: which product type should be preferred? *Vox sanguinis*. 2010; 99 (1), 1-15. Doi: 10.1111/j.1423-0410.2009.01295.x.
43. Hao B, Wang Y, Zhou J, et al. Comparison between the clinical efficacy of platelet concentrates, derived from buffy coat and apheresis in tumor patients. *Oncol Lett*. 2017; 14 (2), 1445-1448. Doi: 10.3892/ol.2017.6270.
44. Bhat A, Chowdappa V and Masamatti SS. Effectiveness of Pooled Platelet Transfusion in Concordant and Discordant Groups among Dengue Patients. *Journal of clinical and diagnostic research : JCDR*. 2016; 10 (7), EC21-EC24. Doi: 10.7860/JCDR/2016/19278.8213.
45. Pietersz RNI. Pooled platelet concentrates: an alternative to single donor apheresis platelets? *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2009; 41 (2), 115-119. Doi: 10.1016/j.transci.2009.07.003.
46. Andreu G, Vasse J, Sandid I, et al. Use of random versus apheresis platelet concentrates. *Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine*. 2007; 14 (6), 514-521. Doi: 10.1016/j.tracli.2008.01.004.
47. Triulzi DJ, Assmann SF, Strauss RG, et al. The impact of platelet transfusion characteristics on posttransfusion platelet increments and clinical bleeding in patients with hypoproliferative thrombocytopenia. *Blood*. 2012; 119 (23), 5553-5562. Doi: 10.1182/blood-2011-11-393165.
48. Slichter SJ, Davis K, Enright H, et al. Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. *Blood*. 2005; 105 (10), 4106-4114. Doi: 10.1182/blood-2003-08-2724.
49. Kopolovic I, Ostro J, Tsubota H, et al. A systematic review of transfusion-associated graft-versus-host disease. *Blood*. 2015; 126 (3), 406-414. Doi: 10.1182/blood-2015-01-620872.
50. Treleaven J, Gennery A, Marsh J, et al. Guidelines on

- the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. *Br J Haematol.* 2011; 152 (1), 35-51. Doi: 10.1111/j.1365-2141.2010.08444.x.
51. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet (London, England).* 2016; 388 (10061), 2825-2836. Doi: 10.1016/S0140-6736(15)01313-6.
  52. Soff GA, Miao Y, Bendheim G, et al. Romiplostim Treatment of Chemotherapy-Induced Thrombocytopenia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2019; 37 (31), 2892-2898. Doi: 10.1200/JCO.18.01931.
  53. Prasanna T, Beith J, Kao S, et al. Dose modifications in adjuvant chemotherapy for solid organ malignancies: A systematic review of clinical trials. *Asia-Pacific journal of clinical oncology.* 2018; 14 (3), 125-133. Doi: 10.1111/ajco.12864.
  54. Elting LS, Rubenstein EB, Martin CG, et al. Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2001; 19 (4), 1137-1146. Doi: 10.1200/JCO.2001.19.4.1137.
  55. Cotreau MM, Stonis L, Strahs A, et al. A multiple-dose, safety, tolerability, pharmacokinetics and pharmacodynamic study of oral recombinant human interleukin-11 (oprelvekin). *Biopharmaceutics & drug disposition.* 2004; 25 (7), 291-296. Doi: 10.1002/bdd.415.
  56. Tepler I, Elias L, Smith JW, 2nd, et al. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood.* 1996; 87 (9), 3607-3614. Doi:
  57. Wilde MI and Faulds D. Oprelvekin: a review of its pharmacology and therapeutic potential in chemotherapy-induced thrombocytopenia. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy.* 1998; 10 (2), 159-171. Doi: 10.2165/00063030-199810020-00006.
  58. Iuliano F, Iuliano E, Perricelli A, et al. Low Doses of Eltrombopag Are Safe and Effective in the Prophylaxis of the Chemotherapy-Induced Thrombocytopenia (CIT). *Blood.* 2016; 128 (22), 4926-4926. Doi: 10.1182/blood.V128.22.4926.4926.
  59. Winer ES, Safran H, Karaszewska B, et al. Eltrombopag for thrombocytopenia in patients with advanced solid tumors receiving gemcitabine-based chemotherapy: a randomized, placebo-controlled phase 2 study. *Int J Hematol.* 2017; 106 (6), 765-776. Doi: 10.1007/s12185-017-2319-9.
  60. Soff GA, Miao Y, Bendheim G, et al. Romiplostim Treatment of Chemotherapy-Induced Thrombocytopenia. *Journal of Clinical Oncology.* 2019; 37 (31), 2892-2898. Doi: 10.1200/jco.18.01931.
  61. Al-Samkari H, Marshall AL, Goodarzi K, et al. The use of romiplostim in treating chemotherapy-induced thrombocytopenia in patients with solid tumors. *Haematologica.* 2018; 103 (4), e169-e172. Doi: 10.3324/haematol.2017.180166.
  62. Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfusion medicine reviews.* 2013; 27 (3), 137-145. Doi: 10.1016/j.tmr.2013.05.005.
  63. Gourley BL, Mesa H and Gupta P. Rapid and complete resolution of chemotherapy-induced thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) with rituximab. *Cancer chemotherapy and pharmacology.* 2010; 65 (5), 1001-1004. Doi: 10.1007/s00280-010-1258-4.
  64. Held-Warmkessel J. Gemcitabine-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Oncol Nurs Forum.* 2014; 41 (5), 551-553. Doi: 10.1188/14.ONF.551-553.
  65. Epperla N, Hemauer K, Hamadani M, et al. Impact of treatment and outcomes for patients with posttransplant drug-associated thrombotic microangiopathy. *Transfusion.* 2017; 57 (11), 2775-2781. Doi: 10.1111/trf.14263.
  66. Lee AYY. Anticoagulation in the treatment of established venous thromboembolism in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009; 27 (29), 4895-4901. Doi: 10.1200/JCO.2009.22.3958.
  67. Samuelson Bannow BR, Lee AYY, Khorana AA, et al. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: A systematic review. *Research and practice in thrombosis and haemostasis.* 2018; 2 (4), 664-669. Doi: 10.1002/rth2.12111.
  68. 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. *Journal of thrombosis and haemostasis : JTH.* 2018; 16 (6), 1246-1249. Doi: 10.1111/jth.14015.