

## 4. BÖLÜM

# ONKOLOJİK TEDAVİYE BAĞLI KARDİYOVASKÜLER KOMPLİKASYONLAR VE PATOFİZYOLOJİSİ

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Onkoloji tedavisindeki gelişmeler sağ kalımı arttırmış olsa da tedaviye bağlı yan etki insidansında da artış görülmüştür.(1,2) En sık görülen yan etkilerden biri de kardiyovasküler hastalıklardır.(3) Bu durum kanser tedavisinin toksik etkisi veya kardiyovasküler riski olan hastalarda sürecin hızlanması şeklinde olabilir.(4)

Kanser tedavisinin kardiyovasküler komplikasyonlarını şu şekilde sınıflayabiliriz;

- Kalp yetmezliği (KY) veya sol ventrikül sistolik disfonksiyonu
- Akut veya kronik koroner arter hastalığı
- Kalp kapak hastalığı
- Bradi/taşiaritmiler
- Sekonder hipertansiyon
- Tromboembolizm
- Periferik vasküler hastalık
- Pulmoner vasküler hastalık ve pulmoner hipertansiyon

Bu bölümde genel hatlarıyla bahsedilecek olan onkolojik tedaviye bağlı kardiyovasküler komplikasyonlar ilerleyen bölümlerde ayrıntılı olarak anlatılacaktır.

## MİYOKART FONKSİYON BOZUKLUĞU VE KALP YETMEZLİĞİ

Miyokart fonksiyon bozukluğu ve kalp yetmezliği, kanser tedavilerine bağlı en sık görülen kardiyovasküler komplikasyonlarıdır. Morbidite ve mortalitede artışa neden olurlar. Kardiyotoksiste akut veya kronik fazda olabilir. Bazı has-

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## KAYNAKLAR

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49:1374–1403.
2. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012;62:220–241.
3. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol* 2015;12:620.
4. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol* 2013;31:3673–3680.
5. Limat S, Daguindau E, Cahn JY, et al. Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. *J Clin Pharm Ther* 2014;39:168–174.
6. Hall PS, Harshman LC, Srinivas S, et al. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. *JACC Heart Fail* 2013;1:72–78.
7. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–1717.
8. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2008;26:3159–3165.
9. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;342:1077–1084.
10. Bristow MR, Thompson PD, Martin RP, et al. Early anthracycline cardiotoxicity. *Am J Med* 1978;65:823–832.
11. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med* 2012;18:1639–1642.
12. Franco VI, Lipshultz SE. Cardiac complications in childhood cancer survivors treated with anthracyclines. *Cardiol Young* 2015;25(Suppl 2):107–116.
13. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991;266:1672–1677.
14. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979;91:710–717.
15. Swain SM, Whaley FS, Ewer MS, et al. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003;97:2869–2879.
16. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213–220.
17. Herrmann J, Lerman A, Sandhu NP, et al. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc* 2014;89:1287–1306.
18. Chow EJ, Chen Y, Kremer LC, et al. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol* 2015;33:394–402.
19. Braverman AC, Antin JH, Plappert MT, et al. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol* 1991;9:1215–1223.
20. Gottdiener JS, Appelbaum FR, Ferrans VJ, et al. Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med* 1981;141:758–763.
21. Gollerkeri A, Harrold L, Rose M, et al. Use of paclitaxel in patients with pre-existing cardiomyopathy: a review of our experience. *Int J Cancer* 2001;93:139–141.
22. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;4:CD006243.
23. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol* 2007;25:3859–3865.

24. Cote GM, Sawyer DB, Chabner BA, et al. ERBB2 inhibition and heart failure. *N Engl J Med* 2012;367:2150–2153.
25. de Azambuja E, Bedard PL, Suter T, et al. Cardiac toxicity with anti-HER-2 therapies: what have we learned so far? *Target Oncol* 2009;4:77–88.
26. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;131:1981–1988.
27. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial. *J Clin Oncol* 2016;34:1034–1042.
28. Cameron D, Brown J, Dent R, et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. *Lancet Oncol* 2013;14:933–942.
29. Motzer RJ, Hutson TE, Celli D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369:722–731.
30. Qi WX, Shen Z, Tang LN, et al. Congestive heart failure risk in cancer patients treated with vascular endothelial growth factor tyrosine kinase inhibitors: a systematic review and meta-analysis of 36 clinical trials. *Br J Clin Pharmacol* 2014;78:748–762.
31. Ewer MS, Suter TM, Lenihan DJ, et al. Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: a comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events. *Eur J Cancer* 2014;50:2162–2170.
32. Force T, Krause DS, Van Etten RA, et al. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nat Rev Cancer* 2007;7:332–344.
33. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol* 2015;33:4210–4218.
34. Shelburne N, Adhikari B, Brell J, et al. Cancer treatment-related cardiotoxicity: current state of knowledge and future research priorities. *J Natl Cancer Inst* 2014;106.
35. Verweij J, Casali PG, Kotasek D, et al. Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: analysis of EORTC-ISG-AGITG study 62005. *Eur J Cancer* 2007;43:974–978.
36. Stewart AK, Rajkumar SV, Dimopoulos MA A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015;372:142–152.
37. Jaworski C, Mariani JA, Wheeler G, et al. Cardiac complications of thoracic irradiation. *J Am Coll Cardiol* 2013;61:2319–2328.
38. Aleman BM, van den Belt-Dusebout AW, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878–1886.
39. Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002;13:797–801.
40. Polk A, Vistisen K, Vaage-Nilsen M, et al. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. *BMC Pharmacol Toxicol* 2014;15:47.
41. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol* 2011;29:3466–3473.
42. Huddart RA, Norman A, Shahidi M, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol* 2003;21:1513–1523.
43. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011;100:167–175.
44. King V, Constine LS, Clark D, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1996;36:881–889.

45. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
46. Storey MR, Munden R, Strom EA, et al. Coronary artery dosimetry in intact left breast irradiation. *Cancer J* 2001;7:492–497.
47. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol* 2016;34:235–243.
48. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med* 2015;175:1007–1017.
49. Hering D, Faber L, Horstkotte D, et al. Echocardiographic features of radiation-associated valvular disease. *Am J Cardiol* 2003;92:226–230.
50. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA* 2003;290:2831–2837.
51. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2014;15:1063–1093.
52. Tamargo J, Caballero R, Delpón E, et al. Cancer chemotherapy and cardiac arrhythmias: a review. *Drug Saf* 2015;38:129–152.
53. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231–2247.
54. Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. *Oncologist* 2013;18:900–908.
55. Milan A, Puglisi E, Ferrari L, et al. Arterial hypertension and cancer. *Int J Cancer* 2014;134:2269–2277.
56. Izzedine H, Ederhy S, Goldwasser F, et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol* 2009;20:807–815.
57. Colt JS, Schwartz K, Graubard BI, et al. Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology* 2011;22:797–804.
58. Lecumberri R, Marques M, Panizo E, et al. High incidence of venous thromboembolism despite electronic alerts for thromboprophylaxis in hospitalised cancer patients. *Thromb Haemost* 2013;110:184–190.
59. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. *Thromb Res* 2006;118:555–568.
60. Di Nisio M, Ferrante N, Feragalli B, et al. Arterial thrombosis in ambulatory cancer patients treated with chemotherapy. *Thromb Res* 2011;127:382–383.
61. Valent P, Hadzijusufovic E, Schernthaner GH, et al. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood* 2015;125:901–906.
62. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst* 2009;101:928–937.
63. Louis EL, McLoughlin MJ, Wortzman G, et al. Chronic damage to medium and large arteries following irradiation. *J Can Assoc Radiol* 1974;25:94–104.
64. Limsuwan A, Pakakasama S, Rochanawutanon M, et al. Pulmonary arterial hypertension after childhood cancer therapy and bone marrow transplantation. *Cardiology* 2006;105:188–194.
65. Farha S, Dweik R, Rahaghi F, et al. Imatinib in pulmonary arterial hypertension: c-Kit inhibition. *Pulm Circ* 2014;4:452–455.
66. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* 2012;125:2128–2137.