

GİRİŞ

Kanser, kalp hastalığı ile birlikte gelişmiş ülkelerde önde gelen mortalite sebebidir. Son zamanlarda kanser tedavisindeki gelişmeler, hastaların hayatta kalma oranlarında artışı sağlamıştır. Kanser tedavisinin kardiyotoksik yan etkileri ise, kanser tedavisi esnasında ve sonrasında artan mortalite ve morbiditeye neden olmaktadır (1). Kanser tedavilerinin kardiyak etkilerinin erken tanımlanması kardiyovasküler toksisite risk değerlendirmesi yapmanın önemini göstermektedir (2). Kanser terapötiklerine bağlı kardiyak fonksiyon bozukluğu insidansı; tedavinin süresi, kullanılan kemoterapötik ajanların tipi ve hasta komorbiditelerine göre geniş bir yelpazede değişkenlik gösterir (3).

Kardiyotoksisite ile en sık ilişkili kemoterapötikler antrasiklinler ve monoklonal antikorlardır . İmmünoterapiler, tirozin kinaz inhibitörleri ve proteazom inhibitörleri gibi yeni ajanlar da kardiyak fonksiyon bozukluğuna neden olabilirler (4).

Kardiyotoksisite

Kardiyak fonksiyon bozukluğuna birçok kemoterapötik ajan neden olabilir. Kanser tedavileri ile ilişkili kardiyovasküler komplikasyonlar arasında kalp yetmezliği (KY), aritmiler, hipertansiyon, akut ve kronik koroner sendromlar, perikardiyal hastalık ve venöz tromboembolizm yer almaktadır (5).

¹ Uzm. Dr., Bayburt Devlet Hastanesi, Kardiyoloji Kliniği, daleesamsun@gmail.com, ORCID iD: 0000-0003-1316-308X



Talidomit tedavisi, hem venöz hem de arteriyel tromboembolik olayların olasılığını artırır (87). Tromboemboliyi önlemek için en iyi yaklaşım olarak aspirin, varfarin veya düşük molekül ağırlıklı heparin önerilmektedir. Talidomit tedavisi altındaki multipl miyelom hastalarının birincil koruması için bu üç antitrombotik ajanın etkinliğini karşılaştıran bir faz III, açık etiketli ve randomize çalışma, hepsinin eşit derecede etkili olduğunu bulmuştur (88). Uluslararası Miyelom Çalışma Grubu, düşük riskli hastalar için aspirin ve yüksek risk altındakiler için terapötik varfarin önermektedir (89). Direkt etkili oral antikoagülan olan apiksaban kullanımının güvenli olduğu ve ilk denemelerde iyi tolere edildiği kanıtlanmıştır ancak talidomit hastaları bağlamında etkinlik açısından değerlendirilmemiştir (90). Talidomit kullanan hastalarda birincil profilaksiste direkt etkili oral antikoagülanların rolünü değerlendirmek için daha geniş ölçekli randomize kontrollü çalışmalara ihtiyaç vardır.

SONUÇ

Kardiyotoksisite, kemoterapinin önemli bir yan etkisidir , bu yüzden kanser hastalarının tedavisinde dikkatli olunmalıdır. Onkolojik tedavi gören her hastada advers kardiyak olay riski iyi değerlendirilmelidir. Hastanın kardiyovasküler öyküsünün, bulunduğu kanser türünün, ihtiyaç duydukları tedavi rejiminin ve mevcut kardiyak profilaktik ve terapötik seçeneklerin iyi değerlendirilmesi gerekir. Gittikçe büyüyen kardiyonkoloji alanı bu karmaşık klinik durumlara özel bakım sağlamak için ortaya çıkmıştır. Optimal hasta sonuçlarını sağlamaya yönelik en uygun yaklaşımı oluşturmak için kanser hastalarında kardiyovasküler bakımı yönetmeye yönelik çeşitli stratejilerin etkinliği hakkında daha fazla araştırmaya ihtiyaç vardır.

KAYNAKLAR

- 1: Michel, L., Rassaf, T., Totzeck, M. Biomarkers for the detection of apparent and subclinical cancer therapy-related cardiotoxicity. *J. Thorac. Dis.* 2018, 10 (Suppl. 35), S4282–S4295.
- 2: Gong, F.F., Cascino, G.J., Murtagh, G., et al. Circulating Biomarkers for Cardiotoxicity Risk Prediction. *Curr. Treat. Options Oncol.* 2021, 22, 46.
- 3: L.B. Thomy, K. Theobald, Cardiotoxicity related to anticancer drug treatment: a literature review, *Aust J Cancer Nurs* 16 (2015) 4–11.
- 4: Vohra, A., Asnani, A. Biomarker Discovery in Cardio-Oncology. *Curr. Cardiol. Rep.* 2018, 20, 52.
- 5: Berliner, D., Beutel, G., Bauersachs, J. Echocardiography and biomarkers for the diagnosis of cardiotoxicity. *Herz* 2020, 45, 637–644.
- 6: Rao, V.U., Reeves, D.J., Chugh, A.R., et al. Clinical Approach to Cardiovascular Toxicity of Oral Antineoplastic Agents: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2021, 77, 2693–2716.



- 7: R Lyon Alexander, Teresa Lopez-Fernández, Liam S. Couch, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European hematology association (eha), the European society for therapeutic radiology and oncology (estro) and the international cardio-oncology society (IC-OS): developed by the task force on cardio-oncology of the European society of Cardiology (ESC), *Eur. Heart J.* 43 (41) (2022) 4229–4361.
- 8: J. Alexandre, J. Cautela, S. Ederhy, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines. *J. Am. Heart Assoc.* 9 (18) (2020 Sep 15), e018403
- 9: P. Thavendiranathan, C. Bucciarelli-Ducci, P. Lancellotti, Multi-modality imaging in the assessment of cardiovascular toxicity in the cancer patient, *JACC Cardiovasc Imaging* 11 (2018) 1173–1186.
- 10: Herrmann, J. Adverse cardiac effects of cancer therapies: Cardiotoxicity and arrhythmia. *Nat. Rev. Cardiol.* 2020, 17, 474–502.
- 11: Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. *Front Cardiovasc Med.* 2020;7:26.
- 12: Fornaro, A., Olivotto, I., Rigacci, L., et al. Comparison of long-term outcome in anthracycline-related versus idiopathic dilated cardiomyopathy: A single centre experience. *Eur. J. Heart Fail.* 2018, 20, 898–906.
- 13: Bojan, A., Torok-Vistai, T., Parvu, A. Assessment and Management of Cardiotoxicity in Hematologic Malignancies. *Dis. Markers.* 2021, 2021, 6616265
- 14: Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardigraphy. *N Engl J Med* 1979;300:278–83.
- 15: Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003;97:2869–79.
- 16: Evaluation of long term cardiotoxicity after epirubicin containing adjuvant chemotherapy and locoregional radiotherapy for breast cancer using various detection techniques *J Heart.* Available at: <https://heart.bmj.com/content/88/1/81>, Accessed June 15, 2023.
- 17: Idarubicin cardiotoxicity: a retrospective study in acute myeloid leukemia and myelodysplasia. *J Clin Oncol* 2022. Available at <https://ascopubs.org/doi/10.1200/JCO.1995.13.11.2827> Accessed June 15,2023.
- 18: Chen MH, Kerkela R, Force T. Mechanisms of cardiomyopathy associated with tyrosine kinase inhibitor cancer therapeutics. *Circulation* 2008;118:84–95.
- 19: Paul MK, Mukhopadhyay AK. Tyrosine kinase role and significance in cancer. *Int J Med Sci* 2004;101–115.
- 20: Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol Stockh Swed* 2009;48:964–970.
- 21: Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet Lond Engl* 2007;370:2011–2019.
- 22: Xu Z, Cang S, Yang T, et al. Cardiotoxicity of tyrosine kinase inhibitors in chronic myelogenous leukemia therapy. *Hematol Rep.* 2009;1:e4
- 23: Cheng M, Yang F, Liu J, et al. Tyrosine kinase inhibitors-induced arrhythmias: from molecular mechanisms, pharmacokinetics to therapeutic strategies. *Front Cardiovasc Med* 2021;8.
- 24: Schramm A, Gregorio ND, Widschwendter P, et al. Targeted therapies in HER2-positive breast cancer - a systematic review. *Breast Care* 2015;10:173–178.
- 25: Yang Z, Wang W, Wang X, et al. Cardiotoxicity of epidermal growth factor receptor 2-targeted drugs for breast cancer. *Front Pharmacol* 2021;12:741451.
- 26: Mohan N, Jiang J, Dokmanovic M, et al. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. *Antib Ther* 2018;1:13–17.
- 27: Nunes AT, Annunziata CM. Proteasome inhibitors: structure and function. *Semin Oncol* 2017;44:377–380.



- 28: Perel G, Bliss J, Thomas CM. Carfilzomib (Kyprolis): a novel proteasome inhibitor for relapsed and/or refractory multiple myeloma. *Pharm Ther* 2016;41:303–307.
- 29: Cole DC, Frishman WH. Cardiovascular complications of proteasome inhibitors used in multiple myeloma. *Cardiol Rev* 2018;26:122–9.
- 30: Lee DH, Fradley MG. Cardiovascular complications of multiple myeloma treatment: evaluation, management, and prevention. *Curr Treat Options Cardiovasc Med* 2018;20:19.
- 31: Ogino MH, Tadi P. Cyclophosphamide. *StatPearls*. StatPearls Publishing; 2022.
- 32: Cardiotoxicity Associated With High-Dose Cyclophosphamide Therapy *JAMA Internal Medicine* *JAMA Network*. Available at: <https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/601073>, Accessed June 15, 2023.
- 33: Dhese S, Chu MP, Blevins G, et al. Cyclophosphamide-induced cardiomyopathy. *J Investig Med High Impact Case Rep* 2013;1:2324709613480346.
- 34: Iqbal A, Iqbal MK, Sharma S, et al. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. *Life Sci* 2019;218:112–31.
- 35: Rowinsky EK, McGuire WP, Guarnieri T, et al. Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991;9:1704–1712.
- 36: McGuire WP, Rowinsky EK, Rosenhein NB, et al. Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989;111:273–279.
- 37: Joshi AM, Prousi GS, Bianco C, et al. Microtubule inhibitors and cardiotoxicity. *Curr Oncol Rep* 2021;23:30.
- 38: Osman M, Elkady M. A prospective study to evaluate the effect of paclitaxel on cardiac ejection fraction. *Breast Care Basel Switz* 2017;12:255–259.
- 39: Patane S. Cardiotoxicity: Cisplatin and long-term cancer survivors. *Int J Cardiol* 2014;175:201–202.
- 40: Mortimer JE, Crowley J, Eyre H, et al. A phase II randomized study comparing sequential and combined intraarterial cisplatin and radiation therapy in primary brain tumors: A southwest oncology group study. *Cancer* 1992;69:1220–1223.
- 41: Tomirotti M, Riundi R, Pulici S, et al. Ischemic cardiopathy from cis-diamminedichloroplatinum (CDDP). *Tumori* 1984;70:235–236.
- 42: Seng S, Liu Z, Chiu SK, et al. Risk of venous thromboembolism in patients with cancer treated with cisplatin: A systematic review and meta-analysis. *J Clin Oncol* 2012;30:4416–4426.
- 43: Lechner D, Kollars M, Gleiss A, et al. Chemotherapy-induced thrombin generation via procoagulant endothelial microparticles is independent of tissue factor activity. *J Thromb Haemost* 2007;5:2445–2452.
- 44: Monreal M, Falga C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency: findings from the RIETE registry. *Am J Med* 2006;119:1073–1079.
- 45: Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–264.
- 46: Lamberti M, Porto S, Zappavigna S, et al. A mechanistic study on the cardiotoxicity of 5-fluorouracil in vitro and clinical and occupational perspectives. *Toxicol Lett* 2014;227:151–156.
- 47: Brell JM. 5-fluorouracil cardiotoxicity: known but unknown. *JACC CardioOncology* 2021;3:110–112.
- 48: Zafar A, Drobni ZD, Mosarla R, et al. The incidence, risk factors, and outcomes with 5-fluorouracil-associated coronary vasospasm. *JACC CardioOncology* 2021;3:101–109.
- 49: Akhtar SS, Salim KP, Bano ZA. Symptomatic cardiotoxicity with high-dose 5-fluorouracil infusion: a prospective study. *Oncology* 1993;50:441–444.
- 50: Zamorano JL, Lancellotti P, Mu~noz DR, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Kardiol Pol* 2016;74(11):1193–1233.



- 51: Anderson KC. Lenalidomide and thalidomide: mechanisms of actionsimilarities and differences. *Semin Hematol* 2005;42(Suppl 4):S3–8.
- 52: Moudgil R, Yeh ETH. Mechanisms of cardiotoxicity of cancer chemotherapeutic agents: Cardiomyopathy and beyond. *Can J Cardiol* 2016;32:863–870.
- 53: Emch GS, Hermann GE, Rogers RC. Tumor necrosis factor-alpha inhibits physiologically identified dorsal motor nucleus neurons in vivo. *Brain Res* 2002;951:311– 315.
- 54: Carver JR, Nasta S, Chong EA, et al. Myocarditis during lenalidomide therapy. *Ann Pharmacother* 2010;44:1840–1843.
- 55: Kaur A, Yu SS, Lee AJ, et al. Thalidomide-induced sinus bradycardia. *Ann Pharmacother* 2003;37:1040–1043.
- 56: Kaushal V, Kohli M, Zangari M, et al. Endothelial dysfunction in antiangiogenesis-associated thrombosis. *J Clin Oncol Off J Am Soc Clin Oncol*. 2002;20 (13):3042–3043.
- 57: Arboscello E, Bellodi A, Passalia C, et al. Thalidomide-induced cardiotoxicity in multiple myeloma patients: An underestimated but clinically relevant issue. *J Clin Oncol* 2010;28(15_suppl):e18544.
- 58: Tan TC, Scherrer-Crosbie M. Assessing the cardiac toxicity of chemotherapeutic agents: role of echocardiography. *Curr Cardiovasc Imaging Rep* 2012;5:403–409.
- 59: Mulvagh SL, Rakowski H, Vannan MA, et al. American society of echocardiography consensus statement on the clinical applications of ultrasonic contrast age echocardiography. *J Am Soc Echocardiogr* 2008;21:1179–1201.
- 60: Pepe A, Pizzino F, Gargiulo P, et al. Cardiovascular imaging in the diagnosis and monitoring of cardiotoxicity: cardiovascular magnetic resonance and nuclear cardiology. *J Cardiovasc Med Hagerstown Md*. 2016;17(Suppl 1):e45–54.
- 61: Perazzolo Marra M, De Lazzari M, Zorzi A, et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm* 2014;11:856–863.
- 62: Zardavas D, Suter TM, Van Veldhuisen DJ, et al. Role of troponins I and T and N -terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy. *J Clin Oncol* 2017;35:878–884.
- 63: Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000;36:517–522.
- 64: Langer SW. Dexrazoxane for the treatment of chemotherapy-related side effects. *Cancer Manag Res* 2014;6:357–363.
- 65: Lyu YL, Kerrigan JE, Lin CP, et al. Topoisomerase IIbeta mediated DNA doublestrand breaks: Implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res* 2007;67:8839–8846.
- 66: Macedo AVS, Hajjar LA, Lyon AR, et al. Efficacy of dexrazoxane in preventing anthracycline cardiotoxicity in breast cancer. *JACC CardioOncology* 2019;1:68–79.
- 67: Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258–2262.
- 68: Chaar M, Kamta J, Ait-Oudhia S. Mechanisms, monitoring, and management of tyrosine kinase inhibitors-associated cardiovascular toxicities. *OncoTargets Ther* 2018;11:6227–3627.
- 69: Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673–1684.
- 70: Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: A report of the american college of cardiology/ American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e876–894.
- 71: Wu P, Oren O, Gertz MA, et al. Proteasome inhibitor-related cardiotoxicity: mechanisms, diagnosis, and management. *Curr Oncol Rep* 2020;22:66.



- 72: Chari A, Hajje D. Case series discussion of cardiac and vascular events following carfilzomib treatment: possible mechanism, screening, and monitoring. *BMC Cancer* 2014;14:915.
- 73: Imam F, Al-Harbi NO, Al-Harbia MM, et al. Rutin attenuates carfilzomib-induced cardiotoxicity through inhibition of NF- κ B, hypertrophic gene expression and oxidative stress. *Cardio-vasc Toxicol* 2017;17:58–66.
- 74: Imam F, Al-Harbi NO, Al-Harbi MM, et al. Apremilast reversed carfilzomib-induced cardiotoxicity through inhibition of oxidative stress, NF- κ B and MAPK signaling in rats. *Toxicol Mech Methods* 2016;26:700–708.
- 75: Al-Harbi NO. Carfilzomib-induced cardiotoxicity mitigated by dexrazoxane through inhibition of hypertrophic gene expression and oxidative stress in rats. *Toxicol Mech Methods* 2016;26:189–195.
- 76: El Kiki SM, Omran MM, Mansour HH, et al. Metformin and/or low dose radiation reduces cardiotoxicity and apoptosis induced by cyclophosphamide through SIRT-1/SOD and BAX/Bcl-2 pathways in rats. *Mol Biol Rep* 2020;47:5115–5126.
- 77: Abd-ElRaouf A, Nada AS, Mohammed NEDA, et al. Low dose gamma irradiation attenuates cyclophosphamide-induced cardiotoxicity in rats: role of NF- κ B signaling pathway. *Int J Radiat Biol* 2021;97:632–641.
- 78: El-Agamy DS, Elkablawy MA, Abo-Haded HM. Modulation of cyclophosphamide-induced cardiotoxicity by methyl palmitate. *Cancer Chemother Pharmacol* 2017;79:399–409.
- 79: Pai VB, Nahata MC. Cardiotoxicity of Chemotherapeutic Agents. *Drug Saf* 2000;22 (4):263–302.
- 80: Hu Y, Sun B, Zhao B, et al. Cisplatin-induced cardiotoxicity with midrange ejection fraction: A case report and review of the literature. *Medicine (Baltimore)* 2018;97:e13807.
- 81: Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231–2247.
- 82: Jiang Debbie, MD, Ian Lee Alfred, MD. Thrombotic Risk from Chemotherapy and Other Cancer Therapies. *Cancer Treat Res* 2019;179:87–101.
- 83: Layoun ME, Wickramasinghe CD, Peralta MV, et al. Fluoropyrimidine-induced cardiotoxicity: manifestations, mechanisms, and management. *Curr Oncol Rep* 2016;18:35.
- 84: Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009;8:191–202.
- 85: Teperikidis E, Boulmpou A, Charalampidis P, et al. 5-Fluorouracil, capecitabine and vasospasm: a scoping review of pathogenesis, management options and future research considerations. *Acta Cardiol* 2022;77:1–13.
- 86: Ma WW, Saif MW, El-Rayes BF, et al. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer* 2017;123:345–356.
- 87: Lee DH, Fradley MG. Cardiovascular complications of multiple myeloma treatment: evaluation, management, and prevention. *Curr Treat Options Cardiovasc Med* 2018;20:19.
- 88: Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2011;29:986–993.
- 89: Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol Off J Am Soc Clin Oncol* 2014;32:587–600.
- 90: Cornell RF, Goldhaber SZ, Engelhardt BG, et al. Primary prevention of venous thromboembolism with apixaban for multiple myeloma patients receiving immunomodulatory agents. *Br J Haematol* 2020;190:555–561.