



ONKOLOJİK TEDAVİYE BAĞLI KALP YETMEZLİĞİNDE TANISAL TESTLER VE YAKLAŞIMLAR

Münevver SARI¹

Onkolojik tedavilerdeki gelişmeler ile hastaların yaşam süreleri uzamıştır. Ancak bu tedavilerin yan etkileri nedeni ile bu hastalarda morbidite ve ölüm sıklığı da artmaktadır. Bu yan etkiler arasında en dikkat çeken onkolojik tedaviler ile ilişkili miyokard fonksiyon bozukluğu ve kalp yetmezliğidir (KY) (1-5). Bu hastaların takibinde miyokard fonksiyon bozukluğu gelişiminden korunmak, geliştiğinde tedaviyi uygun şekilde yönlendirmek ve bu süreçte hastaların onkolojik tedavisinin aksamaması da önemlidir. Bu nedenlerle bu hastaların takibi ve tedavisinin bu konularda deneyimli onkolog ve kardiyologu içeren kardiyo-onkoloji ekibi tarafından yapılmalıdır (1). Onkolojik tedavilere bağlı miyokard fonksiyon bozukluğunun ve KY'nin geliştiği zaman aralığı farklılık göstermektedir; bazı ilaçlarda bu yan etkiler tedavi başladıktan sonra erken dönemde oluşabilirken, bazı tedavilerde uzun dönem sonra ortaya çıkabilmektedir. Ayrıca bazı ilaçlar, antrasiklin grubu gibi erken dönem miyokard hasarı sonrası ilerleyici disfonksiyon ve geç dönemde kardiyomiyopatiye neden olurken, bazı ilaçlar geçici miyokard fonksiyon bozukluğuna neden olabilmektedir (1-5). Çocukluk çağında özellikle antraksin tedavisi ve göğüs bölgesine radyoterapi almış kişilerde yaşam boyu KY riskinin 15 kat arttığı gösterilmiştir (6).

Onkolojik ilaçlara bağlı miyokard fonksiyon bozukluğu ve KY gelişmesi göreceli olarak yaygın ve ciddi bir yan etkidir. Bu yan etki ile ilişkilendirilen onkolojik ilaçlar arasında antrasiklinler (Doxorubicin (Adriamycin), idarubisin, epirubisin, daunorubisin, mitoxanthone, liposomal antrasiklinler), alkileyici ajanlar (siklofosfamid, ifosfamid), antimetabolit ajanlar (clofarabin), antimikrotübül ilaçlar (docetaxel, paclitaxel), monoklonal antikorlar (trastuzumab, bevacizumab, pertuzumab), tirozin kinaz inhibitörleri (sunitinib, pazopanib,

¹ Uzm. Dr. Sağlık Bilimleri Üniversitesi Kartal Koşuyolu Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği benmsr@hotmail.com

tir (44). Carfilzomib ile tedavi edilen hastalarda natriüretik peptidlerin ilk 6 ay içinde yükseldiği özellikle tedavinin ilk 3 haftası içindeki yeni bir yükselmenin 36 kat artmış istenmeyen kardiyovasküler olaylarla ilişkili olduğu görülmüştür. Bu hastalarda istenmeyen kardiyovasküler olaylar tedaviye ara verilmesi ve kötü prognozla ilişkilidir (44). Proteazom inhibitörü verilen hastalarda başlangıçta ve tedavinin erken döneminde natriüretik peptidlerin ölçümü ve takibi ile yüksek riskli hastaların belirlenebileceği vurgulanmıştır (5). Ancak natriüretik peptidlerin özellikle yaşlı ve kadın hastalarda, böbrek yetmezliği olanlarda yüksek olabileceği, obez hastalarda ise düşük saptanabileceği akılda tutulmalıdır (5). Troponin akut kardiyak hasar ile ilişkiliyken, kardiyotoksisitenin uzun dönem takibinde natriüretik peptidlerin kullanımı öne çıkmaktadır.

Ekokardiyografi ve biyobelirteçler kullanılarak kardiyotoksisite tarama ve takibinin zamanlaması, hastanın bazal kardiyovasküler riskleri ve spesifik onkolojik tedavi protokolü dikkate alınarak her hastada bireysel olarak yapılmalıdır. Onkolojik tedavi süresince asemptomatik sol ventrikül fonksiyon bozukluğu ve KY gelişen hastalar ACE inhibitörü veya anjiyotensin reseptör blokleri ve betablokerler ile tedaviden fayda görmektedirler. Antrasiklin tedavisine bağlı miyokard fonksiyon bozukluğu gelişen hastalarda erken dönemde ACE inhibitörü ve/veya betabloker tedavi başlanması ile daha iyi uzun dönem sonuçlara sahip oldukları gösterilmiştir (45).

KAYNAKLAR

1. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(36):2768-2801.
2. Curigliano G, Lenihan D, Fradley M, et al. ESMO Guidelines Committee. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31(2):171-190.
3. Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020;22(9):1504-1524.
4. Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, et al. Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient. *JACC Cardiovasc Imaging*. 2018;11(8):1173-1186.
5. Ananthan K, Lyon AR. The Role of Biomarkers in Cardio-Oncology. *J Cardiovasc Transl Res*. 2020;13(3):431-450.
6. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572-1582.

7. 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. *J Am Soc Echocardiogr.* 2014;27: 911–39.
8. Ali MT, Yucel E, Bouras S, et al. Myocardial strain is associated with adverse clinical cardiac events in patients treated with anthracyclines. *J Am Soc Echocardiogr.* 2016;29:522–527.
9. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation.* 2015;131:1981–1988.
10. 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.
11. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer.* 2003;97:2869–2879.
12. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* 2007;25:3808–3815.
13. Gottdiener JS, Appelbaum FR, Ferrans VJ, et al. Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med.* 1981;141:758–763.
14. 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.
15. 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.
16. 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.
17. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol.* 2010;28:3910–3916.
18. 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.
19. Steingart RM, Bakris GL, Chen HX, et al. Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *Am Heart J.* 2012;163:156–163.
20. 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.
21. 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.
22. Russell SD, Lyon A, Lenihan DJ, et al. Serial echocardiographic assessment of patients with relapsed multiple myeloma (RMM) receiving carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd): a substudy of the phase 3 Endeavor Trial (NCT01568866). *Blood.* 2015;126:abstract 4250.
23. Moslehi JJ, Salem JE, Sosman JA, et al. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet.* 2018;391:933.
24. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *Journal of the American College of Cardiology.* 2018;71(16):1755–1764.
25. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *The New England Journal of Medicine.* 2016;375(18):1749–1755.
26. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *Journal of the American College of Cardiology.* 2019;74(25):3099–3108.

27. 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.
28. Zhang KW, Finkelman BS, Gulati G, et al. Abnormalities in 3-dimensional left ventricular mechanics with anthracycline chemotherapy are associated with systolic and diastolic dysfunction. *J Am Coll Cardiol Img*.2018;11:1059-68.
29. Negishi K, Negishi T, Hare JL, et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr*.2013;26:493-8.
30. Negishi K, Negishi T, Haluska BA, et al. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging*.2014;15:324-331.
31. Charbonnel C, Convers-Domart R, Rigaudeau S,et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. *Eur Heart J Cardiovasc Imaging*.2017;18:392-401.
32. Bergamini C, Dolci G, Rossi A, et al. Left atrial volume in patients with HER2-positive breast cancer: One step further to predict trastuzumab-related cardiotoxicity. *Clin Cardiol*. 2018;41(3):349-353. doi:10.1002/clc.22872
33. Sarocchi M, Bauckneht M, Arboscello E, et al. An increase in myocardial 18-fluorodeoxyglucose uptake is associated with left ventricular ejection fraction decline in Hodgkin lymphoma patients treated with anthracycline. *J Transl Med*.2018;16:295.
34. CardinaleD, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *Journal of the American College of Cardiology*. 2000;36(2):517-522.
35. CardinaleD, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109(22):2749-2754.
36. ZardavasD, 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 2-positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy. *Journal of Clinical Oncology*. 2017;35(8):878-884
37. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*.2012;5:596-603.
38. Ylänen K, Poutanen T, Savukoski T, et al. Cardiac biomarkers indicate a need for sensitive cardiac imaging among long-term childhood cancer survivors exposed to anthracyclines. *Acta Paediatrica*. 2015;104(3):313-319.
39. Pourier MS, Kapusta L, van Gennip A, et al. Values of high sensitive troponin T in long-term survivors of childhood cancer treated with anthracyclines. *Clinica Chimica Acta*.2015;441:29-32
40. Wieshammer S, Dreyhaupt J, Müller D, et al. Limitations of N-terminal pro-B-type natriuretic peptide in the diagnosis of heart disease among cancer patients who present with cardiac or pulmonary symptoms. *Oncology*. 2016;90(3):143-150.
41. Pavo N, Raderer M, Hülsmann M, et al. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. *Heart* 2015;101(23):1874-1880.
42. Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? *Clinical Chemistry*. 2005;51(8):1405-1410.
43. Lenihan DJ, Stevens PL, Massey M, et al. The utility of point-of-care biomarkers to detect cardiotoxicity during anthracycline chemotherapy: a feasibility study. *Journal of Cardiac Failure*. 2016;22(6):433-438.

44. Cornell RF, Ky B, Weiss BM, et al. Prospective study of cardiac events during proteasome inhibitor therapy for relapsed multiple myeloma. *Journal of Clinical Oncology*. 2019;37(22):1946–1955.
45. 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.