

Bölüm 23

KEMOTERAPİ VE KARDİYOTOKSİSİTE: TANI, TEDAVİ VE KORUMA

Bülent ÖZLEK¹

GİRİŞ

Yirminci yüzyılın başlarından itibaren bulaşıcı hastalıkların önlenmesi ve tedavisindeki gelişmeler, daha iyi hijyen, iyileşmiş sosyoekonomik koşullar ve bunun sonucu olarak yaşam süresinin uzaması nedeniyle; kardiyovasküler, serebrovasküler hastalıklar ve kanser önde gelen ölüm nedenleri haline gelmiştir. Kardiyovasküler hastalıklara bağlı ölümü önleme çabaları etkili olduğu için, kanser ölümün ana nedeni olarak giderek artış göstermektedir (Albini & Sporn, 2007). Son yıllarda kanser tarama yöntemlerinin geliştirilmesi ile erken tanı konabilmekte ve adjuvan kemoterapi kullanımının yaygınlaşması ile kanser tedavisinde de şifa oranı belirgin olarak artmaktadır. Bununla birlikte, neoplastik ya da preneoplastik bir durum nedeniyle kemoterapi gören hastalar kardiyovasküler sağlığın bozulması açısından önemli bir risk taşımaktadır. Kardiyotoksiste; “kemoterapi kaynaklı kardiyak yan etkilerin tümü” olarak tanımlanmaktadır. Kardiyotoksiste, her kür sırasında uygulanan doza veya toplam kümülatif doza bağlı olabileceği gibi dozdan tamamen bağımsız da olabilir. İlk kez 1967 yılında doksorubisin ile tedavi edilen çocuklarda kalp yetersizliği (KY) rapor edilmiş ve sonrasında da kanser hastalarındaki uzun yaşam beklentisine karşın, kanser ilaçlarının yapmış oldukları kardiyak yan etkiler gittikçe ilgi çeken bir konu olmuştur (Tan & ark., 1967, Yeh ET, 2006). Kemoterapi kaynaklı kardiyotoksik etkiler; geçici, hafif bir kan basıncı yüksekliği ve/veya basit elektrokardiyografi (EKG) değişikliklerinden ölümcül, ciddi aritmilere; miyokardit ve/veya perikarditten akut miyokard enfarktüsü ve KY’ye varan geniş bir spektrum göstermektedir. Ayrıca kanser vakalarının görülme yaşı dikkate alındığında bu yaş grubunda hipertansiyon, koroner arter hastalığı, KY ve diğer kalp hastalıklarının görülme sıklığı da yüksektir. O nedenle kanser tedavisi ile takip edilen çoğu hasta, tümör rekürrensinden daha çok kardiyovasküler nedenlerden dolayı ölmektedir (Kha-koo & Yeh, 2008).

¹ Uzman Dr, Muğla Sıtkı Koçman Üniversitesi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, bulent_ozlek@hotmail.com

potansiyel kardiyak etkiyi azaltmaya çalışması da gerekmektedir. Kemoterapötik ajanların kardiyotoksik etkileri her ne kadar nadir gözükse de, ortaya çıktığı anda kanser hastalarında daha fazla morbidite ve mortaliteye neden olmaktadır. Kardiyovasküler yan etkilerin ortaya çıkmaması ve mevcut olan hastalığı daha da kötüleştirmemesi için kardiyologların ve onkologların yakın takip ve işbirliği yapması elzemdir. Bu sebeple, kardiyotoksik etkilerin en sık görüldüğü kemoterapötikler, olası kardiyotoksik etkiler, hastayı bu etkilerden korumak için yapılabilecekler ve tedavi yönetimi klinisyenler için büyük önem arz etmektedir.

KAYNAKÇA

- Advani PP, Ballman KV, Dockter TJ & ark. (2016) Long-Term Cardiac Safety Analysis of NCCTG N9831 (Alliance) Adjuvant Trastuzumab Trial. *J Clin Oncol*, 34:581–587.
- Albini A, Pennesi G, Donatelli F & ark. (2010) Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*, 102(1):14-25. doi: 10.1093/jnci/djp440.
- Albini A, Sporn MB. (2007) The tumour microenvironment as a target for chemoprevention. *Nat Rev Cancer*, 7(2):139– 147.
- Berliner S, Rahima M, Sidi Y & ark. (1990) Acute coronary events following cisplatin-based chemotherapy. *Cancer Invest*, 8:583-6.
- Billingham MEBM. (1984) Evaluation of anthracycline cardiotoxicity: predictive ability and functional correlation of endomyocardial biopsy. *Cancer Treat Symp*, 3:71-6.
- Bosch X, Rovira M, Sitges M & ark. (2013) Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant hemopathies). *J Am Coll Cardiol*, 61:2355–2362.
- Bowles EJ, Wellman R, Feigelson HS & ark. (2012) Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*, 104:1293–1305.
- Bristow MR, Thompson PD, Martin RP & ark. (1978) Early anthracycline cardiotoxicity. *Am J Med*, 65:823-32.
- Cardinale D, Colombo A, Lamantia G & ark. (2010) Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*, 55:213–220.
- Cardinale D, Sandri MT, Martinoni A & ark. (2000) Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*, 36:517–522.
- Cardinale D, Sandri MT. (2010) Role of biomarkers in chemotherapy-induced cardiotoxicity. *Prog Cardiovasc Dis*, 53:121–129.
- Chen MH, Kerkela R, Force T. (2008) Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. *Circulation*, 118:84-95.
- Clarke E, Lenihan D. (2015) Cardio-oncology: a new discipline in medicine to lead us into truly integrative care. *Future Cardiol*, 11:359–361.
- Crone SA, Zhao YY, Fan L & ark. (2002) ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med*, 8(5):459-65.

- Dasari S, Tchounwou PB. (2014) Cisplatin in cancer therapy: molecular mechanisms of action. *Eur J Pharmacol*, 740:364-78. doi: 10.1016/j.ejphar.2014.07.025.
- de Azambuja E, Procter MJ, van Veldhuisen DJ & ark. (2014) Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). *J Clin Oncol*, 32:2159–2165.
- deForni M, Malet-Martino MC, Jaillais P & ark. (1992) Cardiotoxicity of high dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol*, 10:1795-801.
- Dent SF, Graham NA. (2011) First annual Canadian Cardiac Oncology Network conference. *Curr Oncol*, 18:295-300.
- Floyd JD, Nguyen DT, Lobins RL & ark. (2005) Cardiotoxicity of cancer therapy. *J Clin Oncol*, 23(30):7685-96
- Friedman MA, Bozdech MJ, Billingham ME & ark. (1978) Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. *JAMA*, 240:1603-6.
- Glück S. (2005) Adjuvant chemotherapy for early breast cancer: optimal use of epirubicin. *Oncologist*, 10(10):780-91.
- Goldberg MA, Antin JH, Guinan EC & ark. (1986) Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood*, 68:1114-8.
- Gottdiener JS, Appelbaum FR, Ferrans VJ & ark. (1981) Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med*, 141:758-63.
- Gradishar WJ, Vokes EE. (1991) 5-Fluorouracil cardiotoxicity: a critical review. *Ann Oncol*, 1:409-14.
- Gulati G, Heck SL, Ree AH & ark. (2016) Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebocontrolled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J*, 37:1671–1680.
- Gwee MC, Cheah LS. (1986) Actions of cimetidine and ranitidine at some cholinergic sites: implications in toxicology and anesthesia. *Life Sci*, 39(5):383-8.
- Hensley ML, Schuchter LM, Lindley C & ark. (1999) American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol*, 17:3333-55.
- Jones LW, Liu Q, Armstrong GT & ark. (2014) Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*, 32:3643–3650.
- Khakoo AY, Yeh ET. (2008) Management of cardiovascular disease in patients with cancer and cardiac complications of cancer therapy. *Nat Clin Pract Oncol*, 5:655-67.
- Labianca R, Beretta G, Clerici M & ark. (1982) Cardiotoxicity of 5-FU: A study of 1083 patients. *Tumori*, 68:505-10.
- Lewis AB, Crouse VL, Evans W & ark. (1981) Recovery of left ventricular function following discontinuation of anthracycline chemotherapy in children. *Pediatrics*, 68:67-72.
- McGowan JV, Chung R, Maulik A & ark. (2017) Anthracycline chemotherapy and cardiotoxicity. *Cardiovasc Drugs Ther*, 31(1):63-75. doi: 10.1007/s10557-016-6711-0.
- McKillop JH, Bristow MR, Goris ML & ark. (1983) Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. *Am Heart J*, 106:1048-56.
- Moja L, Tagliabue L, Balduzzi S & ark. (2012) Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*, 4:CD006243.
- Moreb JS, Oblon DJ. (1992) Outcome of clinical congestive heart failure induced by anthracycline chemotherapy. *Cancer*, 70:2637-41.
- Myers C, Bonow R, Palmeri S & ark. (1983) A randomized controlled trial assessing the

- prevention of doxorubicin cardiomyopathy by N-acetylcysteine. *Semin Oncol*, 10(1 Suppl 1):53-5.
- Outomuro D, Grana DR, Azzato F & ark. (2007) Adriamycin-induced myocardial toxicity: new solutions for an old problem? *Int J Cardiol*, 117(1):6-15.
- Rosenfeld CS, Broder LE. (1984) Cisplatin-induced autonomic neuropathy. *Cancer Treat Rep*, 68:659-60.
- Rowinsky EK, McGuire WP, Guarnieri T & ark. (1991) Cardiac disturbances during the administration of taxol. *J Clin Oncol*, 9:1704-12.
- Sanani S, Spaulding MB, Masud AR & ark. (1981) 5-FU cardiotoxicity. *Cancer Treat Rep*, 65:1123-5.
- Schimmel KJ, Richel DJ, van den Brink RB & ark. (2004) Cardiotoxicity of cytotoxic drugs. *Cancer Treat Rev*, 30(2):181-191.
- Schwartz RG, McKenzie WB, Alexander J & ark. (1987) Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiology. *Am J Med*, 82:1109-18.
- Seidman A, Hudis C, Pierri MK & ark. (2002) Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*, 20(5):1215-1221.
- Seymour L, Bramwell V, Moran LA. (1999) Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer. The Provincial Systemic Treatment Disease Site Group. *Cancer Prev Control*, 3(2):145-59.
- Singal PK, Iliskovic N. (1998) Doxorubicin-induced cardiomyopathy. *N Engl J Med*, 339(13):900-5.
- Slørdal L, Spigset O. (2006) Heart failure induced by non-cardiac drugs. *Drug Saf*, 29(7):567-86.
- Speyer JL, Green MD, Zeleniuch-Jacquotte A & ark. (1992) ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. *J Clin Oncol*, 10:117-27.
- Suter TM, Procter M, van Veldhuisen DJ & ark. (2007) Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*, 25:3859-3865.
- Swain SM, Whaley FS, Ewer MS. (2003) Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*, 97(11):2869-79.
- Tan C, Tasaka H, Kou-Ping Y & ark. (1967) Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease: clinical evaluation with special reference to childhood leukemia. *Cancer*, 20:33353.
- Thakur A, Witteles RM. (2014) Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. *J Card Fail*, 20:155-158.
- Thavendiranathan P, Wintersperger BJ, Flamm SD & ark. (2013) Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. *Circ Cardiovasc Imaging*, 6:1080-1091.
- Verweij J, Funke-Kupper AJ, Teule GJ & ark. (1988) A prospective study on the dose dependency of cardiotoxicity induced by mitomycin C. *Med Oncol Tumor Pharmacother*, 5:159-63.
- Villani F, Comazzi R, Lacaita G & ark. (1985) Possible enhancement of the cardiotoxicity of doxorubicin when combined with mitomycin C. *Med Oncol Tumor Pharmacother*, 2:93-7.
- Wouters KA, Kremer LC, Miller TL & ark. (2005) Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol*, 131(5):561-78.

- Yeh ET. (2006) Cardiotoxicity induced by chemotherapy and antibody therapy. *Annu Rev Med*, 57:485-98.
- Youssef G, Links M. (2005) The prevention and management of cardiovascular complications of chemotherapy in patients with cancer. *Am J Cardiovasc Drugs*, (4):233-43.
- Zamorano JL, Lancellotti P, Rodriguez Muñoz D & ark. (2017) 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 J Heart Fail*, 19(1):9-42. doi: 10.1002/ejhf.654.