

25. BÖLÜM

MONOKLONAL ANTİKORLAR VE KALP YETERSİZLİĞİ

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GİRİŞ

Hedefe yönelik tedaviler günümüzde konvansiyonel kemoterapilere ek olarak ya da tek başlarına birçok kanser türünde kullanılmaktadır. Hedeflenebilir bir reseptöre karşı geliştirilen antikor komplekslerine monoklonal antikor (mAB), bu reseptörlerin intrasellüler tirozin kinaz aktivitesini ve bu sayede intrasellüler sinyal iletimini inhibe eden moleküllere de tirozin kinaz inhibitörleri (TKİ) denilmektedir.

Günümüzde monoklonal antikorlar birçok kanser türünde onkolojik tedavinin yapı taşları içerisinde yer almaktadır. Kanser tedavisinde kullanılan konvansiyonel ilaç gruplarında olabileceği gibi mAB kullanımında da kardiyotoksikite riski mevcuttur. Kardiyovasküler yan etkilerden en sık hipertansiyon, kardiyak iskemi, tromboz, ve KY görülmektedir. Özellikle altta yatan kardiyak komorbidite varlığında bu risk artmaktadır.

Son on yılda saptanan yeni hedefler ve bu doğrultuda geliştirilen yeni tedavi modaliteleri ile birlikte kanser hastalarında yaşam uzamıştır. Bu uzamanın yanında hastaları olası kardiyovasküler yan etkilerden kısa ve uzun dönemde ko-

rumak, yan etkiyi erken fark etmek ve yönetebilmek medikal onkoloji ve kardiyoloji branşlarının multidisipliner çalışması ile mümkündür.

MOLEKÜLER MEKANİZMA VE ETKİLER

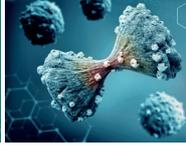
Monoklonal antikorların kardiyotoksikite oluşturmadaki iki temel mekanizma Vasküler Endotelial Büyüme Faktörü (VEGF) hedeflenerek anjiogenez üzerine olan etkinlikleri ve İnsan Epidermal Büyüme Faktörü 2 (HER2) üzerinden gerçekleşen etkinlikleridir¹. HER2 ve VEGFR hedefli tedavilerde kısa dönem ve uzun dönem kardiyovasküler yan etkiler açısından dikkatli olunmalıdır.

VEGF Reseptör Hedefli Tedaviler

VEGF ailesi beş temel proteinden oluşur ve bunlardan en aktif olanı VEGF-A olup sıklıkla VEGF reseptör (VEGFR) 1-2 reseptörlerini hücre içi sinyal iletiminde hedef olarak kullanır. Bu reseptörler normal endotelial hücrelerde mev-

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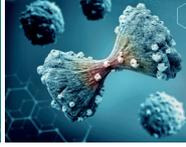


larında kardiyovasküler sistem üzerine tanımlanmış yan etkileri mevcuttur. Ancak bu yan etkileri iyi tanımlamak, önleyebilmek, önlenemese dahi erken tespit edebilmek ve hastanın yaşam kalitesini bozmayacak şekilde yönetebilmek medikal onkoloji ve kardiyoloji hekimlerinin multi-disipliner değerlendirmesi ile mümkün olabilen bir süreçtir.

KAYNAKLAR

1. Wu Q, Bai B, Tian C, et al. The Molecular Mechanisms of Cardiotoxicity Induced by HER2, VEGF, and Tyrosine Kinase Inhibitors: an Updated Review. *Cardiovasc Drugs Ther.* 2021;1-14.
2. Li M, Kroetz DL. Bevacizumab-induced hypertension: Clinical presentation and molecular understanding. *Pharmacol Ther.* 2018;182:152-160.
3. Neagoe P-E, Lemieux C, Sirois MG. Vascular endothelial growth factor (VEGF)-A165-induced prostacyclin synthesis requires the activation of VEGF receptor-1 and-2 heterodimer. *J Biol Chem.* 2005;280(11):9904-9912.
4. Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. *Nature reviews Molecular cell biology.* 2016;17(10):611.
5. Plummer C, Michael A, Shaikh G, et al. Expert recommendations on the management of hypertension in patients with ovarian and cervical cancer receiving bevacizumab in the UK. *Br J Cancer.* 2019;121(2):109-116.
6. Steeghs N, Rabelink T, Op't Roodt J, et al. Reversibility of capillary density after discontinuation of bevacizumab treatment. *Ann Oncol.* 2010;21(5):1100-1105.
7. Fernández Montes A, Martínez Lago N, Cove-la Rúa M, et al. Efficacy and safety of FOLFIRI/aflibercept in second-line treatment of metastatic colorectal cancer in a real-world population: Prognostic and predictive markers. *Cancer medicine.* 2019;8(3):882-889.
8. Roviello G, Pacifico C, Corona P, Generali D. Risk of hypertension with ramucirumab-based therapy in solid tumors: data from a literature based meta-analysis. *Invest New Drugs.* 2017;35(4):518-523.
9. Shiojima I, Sato K, Izumiya Y, et al. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. *The Journal of clinical investigation.* 2005;115(8):2108-2118.
10. Qi W-X, Fu S, Zhang Q, Guo X-M. Bevacizumab increases the risk of severe congestive heart failure in cancer patients: an up-to-date meta-analysis with a focus on different subgroups. *Clin Drug Invest.* 2014;34(10):681-690.
11. Totzeck M, Mincu RI, Rassaf T. Cardiovascular adverse events in patients with cancer treated with bevacizumab: a meta-analysis of more than 20 000 patients. *Journal of the American Heart Association.* 2017;6(8):e006278.
12. Tabernero J, Hozak R, Yoshino T, et al. Analysis of angiogenesis biomarkers for ramucirumab efficacy in patients with metastatic colorectal cancer from RAISE, a global, randomized, double-blind, phase III study. *Ann Oncol.* 2018;29(3):602-609.
13. Pentheroudakis G, Kotoula V, Koliou G-A, et al. AMALTHEA: Prospective, single-arm study of the Hellenic Cooperative Oncology Group (HeCOG) evaluating efficacy and safety of first-line FOLFIRI+ aflibercept for 6 months followed by aflibercept maintenance in patients with metastatic colorectal cancer. *Clin Colorectal Cancer.* 2018;17(4):e631-e637.
14. Ferroni P, Formica V, Roselli M, Guadagni F. Thromboembolic events in patients treated with anti-angiogenic drugs. *Curr Vasc Pharmacol.* 2010;8(1):102-113.
15. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA.* 2008;300(19):2277-2285.
16. Kanukula R, Ganta S, Sirumalla Y, Salam A, Baddam R, Pasupuleti BC. Risk of Venous Thromboembolic Events in Patients With Cancer Treated With Aflibercept: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am J Ther.* 2019;26(4):e549-e552.
17. Arnold D, Fuchs C, Tabernero J, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. *Ann Oncol.* 2017;28(12):2932-2942.
18. D'Uva G, Aharonov A, Lauriola M, et al. ERBB2 triggers mammalian heart regeneration by pro-

- moting cardiomyocyte dedifferentiation and proliferation. *Nat Cell Biol.* 2015;17(5):627-638.
19. Rohrbach S, Muller-Werdan U, Werdan K, Koch S, Gellerich NF, Holtz J. Apoptosis-modulating interaction of the neuregulin/erbB pathway with anthracyclines in regulating Bcl-xS and Bcl-xL in cardiomyocytes. *J Mol Cell Cardiol.* 2005;38(3):485-493.
 20. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA.* 2019;321(3):288-300.
 21. Chen T, Xu T, Li Y, et al. Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis. *Cancer Treat Rev.* 2011;37(4):312-320.
 22. Naaktgeboren W, Linschoten M, de Graeff A, et al. Long-term cardiovascular health in adult cancer survivors. *Maturitas.* 2017;105:37-45.
 23. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *The Lancet Oncology.* 2020;21(4):519-530.
 24. Dobbin SJ, Cameron AC, Petrie MC, Jones RJ, Touyz RM, Lang NN. Toxicity of cancer therapy: what the cardiologist needs to know about angiogenesis inhibitors. *Heart.* 2018;104(24):1995-2002.
 25. Hamnvik OPR, Choueiri TK, Turchin A, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer.* 2015;121(2):311-319.
 26. Cai J, Ma H, Huang F, et al. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. *World J Surg Oncol.* 2013;11(1):1-8.
 27. Hurwitz HI, Douglas PS, Middleton JP, et al. Analysis of early hypertension and clinical outcome with bevacizumab: results from seven phase III studies. *The oncologist.* 2013;18(3):273.
 28. Ruf R, Yarandi N, Ortiz-Melo DI, Sparks MA. Onco-hypertension: Overview of hypertension with anti-cancer agents. *Journal of Onco-Nephrology.* 2021;23993693211001374.
 29. Bottinor WJ, Shuey MM, Manouchehri A, et al. Renin-angiotensin-aldosterone system modulates blood pressure response during vascular endothelial growth factor receptor inhibition. *Cardio Oncology.* 2019;1(1):14-23.
 30. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 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.
 31. Ozturk M, Ozler M, Kurt YG, et al. Efficacy of melatonin, mercaptoethylguanidine and 1400W in doxorubicin-and trastuzumab-induced cardiotoxicity. *J Pineal Res.* 2011;50(1):89-96.
 32. Riccio G, Antonucci S, Coppola C, et al. Ranolazine attenuates trastuzumab-induced heart dysfunction by modulating ROS production. *Front Physiol.* 2018;9:38.
 33. Löffler AI, Salerno M. Cardiac MRI for the evaluation of oncologic cardiotoxicity. *J Nucl Cardiol.* 2018;25(6):2148-2158.
 34. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30(8):1194-1220.
 35. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol.* 2002;20(5):1215-1221.
 36. 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. *European Heart Journal-Cardiovascular Imaging.* 2014;15(10):1063-1093.
 37. Dobson R, Ghosh AK, Ky B, et al. British Society for Echocardiography and British Cardio-Oncology Society guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. *Echo Research and Practice.* 2021;8(1):G1-G18.
 38. Ohtani K, Ide T, Hiasa K-i, et al. Cardioprotective effect of renin-angiotensin inhibitors and β -blockers in trastuzumab-related cardiotoxicity. *Clin Res Cardiol.* 2019;108(10):1128-1139.
 39. Calvillo-Argüelles O, Abdel-Qadir H, Michalowska M, et al. Cardioprotective effect of statins in patients with HER2-positive breast cancer



- receiving trastuzumab therapy. *Can J Cardiol.* 2019;35(2):153-159.
40. Cho D-H, Lim I-R, Kim J-H, et al. Protective Effects of Statin and Angiotensin Receptor Blocker in a Rat Model of Doxorubicin-and Trastuzumab-Induced Cardiomyopathy. *J Am Soc Echocardiogr.* 2020;33(10):1253-1263.
41. Scappaticci FA, Skillings JR, Holden SN, et al. Arteriyal thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst.* 2007;99(16):1232-1239.
42. Mitsuhashi T, Uemoto R, Ishikawa K, et al. Endothelial Nitric Oxide Synthase-Independent Pleiotropic Effects of Pitavastatin Against Atherogenesis and Limb Ischemia in Mice. *Journal of atherosclerosis and thrombosis.* 2017:37747.
43. Chen Y, Zhang S, Peng G, et al. Endothelial NO synthase and reactive oxygen species mediated effect of simvastatin on vessel structure and function: pleiotropic and dose-dependent effect on tumor vascular stabilization. *Int J Oncol.* 2013;42(4):1325-1336.
44. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378(7):615-624.
45. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol.* 2018.