Bölüm
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RADYOTERAPİ VE İMMÜNOTERAPİ İLİŞKİSİ

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GİRİŞ

Radyoterapi (RT) kanser tedavisinin önemli bileşenlerinden biridir. Hastaların yaklaşık 2/3'üne tedavileri sırasında küratif ya da palyatif amaçlı RT uygulanır. RT, DNA hasarı yaparak başlıca lokal etki gösterir. Preklinik çalışmalar iyonize radyasyonun tümör hücrelerinde immünolojik hücre ölümü şeklinde antitümoral etki gösterdiğini ortaya çıkarmıştır. Radyasyonun sistemik etkisi ise rutin klinik uygulamada, yorgunluk, anoreksi gibi belirtilerle karşımıza çıkar. Bu etkilerin radyasyonun indüklediği inflamatuar sitokinler aracılığıyla gerçekleştiği düşünülmektedir (1).

Konağa yabancı yapılara karşı direnci sağlayan hücrelerin, dokuların ve moleküllerin oluşturduğu bütüne immün sistem; bu hücrelerin ve moleküllerin oluşturdukları koordineli reaksiyonlara immün yanıt denir. İmmün yanıt doğal ve edinsel olmak üzere başlıca 2 kısma ayrılır; doğal bağışıklık saatler içinde ortaya çıkar ve kompleman, sitokin, makrofaj, nötrofil ve doğal öldürücü hücreler (Naturel Killer, NK) aracılığıyla aktive olur. Edinsel bağışıklık ise bellek yapısına sahiptir, günler içinde ortaya çıkar; antikorlar, T ve B hücreleri aracılık eder.

İmmünoterapi (İT), metastatik melanom ve renal hücreli karsinomlu hastalara sağladığı sağkalım katkısından sonra birçok kanser türünde denenmiştir. İT ile uzun süreli kalıcı cevap elde edilebilse de birçok tümör tipi nihayetinde tedaviye direnç geliştirerek progrese olur (2). Bu nedenle, yanıt oranlarını en üst düzeye çıkarmak için hem sistemik hem de lokal diğer ajanlarla birleştirilmesi uygun bir yaklaşım gibi görünmektedir. Bu bağlamda İT-RT kombinasyonu, birçok prekli-

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SONUÇ

Özetle, RT'nin İT ile birlikte kullanımı başlıca antijen görünülürlüğünü arttırmak, STING yolağını aktive etmek ve tümör mikroçevresini düzenlemek gibi mekanizmalarla sinerjistik etkiye neden olmaktadır. Tedavi kombinasyonunun etkinliği birçok preklinik çalışma ve umut veren klinik çalışmalar ile ortaya konmuş olmasına rağmen, hala birçok bilinmezlik içerir. Özellikle RT doz ve zamanlaması ileri çalışmalarla desteklenmelidir.

Anahtar Kelimeler: radyoterapi, immünoterapi

KAYNAKÇA

1. Siva S, Macmanus M, Martin R et al. Abscopal effects of radiation therapy: A clinical review for the radiobiologist. Cancer Letters. 2013;356(1):82-90
2. Restifo N.P, Smyth M.J, Snyder A. Acquired resistance to immunotherapy and future challenges. Nat. Rev. Cancer**.** 2016;16(2):121–126.
3. Ngwa, W. et al. Using immunotherapy to boost the abscopal effect. Nat. Rev. Cancer 2018;18(5):313–322.
4. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of nonsmall-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1trial. Lancet Oncol 2017;18(7):895–903.
5. Wang Y, Deng W, Li N et al. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front Pharmacol. 2018;9:185
6. Sharp HJ, Wansley EK, Garnett CT, et al. Synergistic antitumor activity of immune strategies combined with radiation. Front Biosci 2007;12:4900–4910.
7. Kwilas AR, Donahue RN, Bernstein MB, et al. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. Front Oncol 2012;2:104.
8. Price JG, Idoyaga J, Salmon H, et al. CDKN1A regulates Langerhans cell survival and promotes Treg cell generation upon exposure to ionizing irradiation. Nat Immunol 2015;16(10):1060–1068.
9. Albert ML, Pearce SF, Francisco LM, et al. Immature dendritic cells phagocytose apoptotic cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J Exp Med 1998;188(7):1359–1368.
10. Harshyne LA, Watkins SC, Gambotto A, et al. Dendritic cells acquire antigens from live cells for cross-presentation to CTL. J Immunol 2001;166(6):3717–3723.
11. Heath WR, Carbone FR. Cross-presentation, dendritic cells, tolerance and immunity. Annu Rev Immunol 2001;19:47–64.
12. Kaur P, and Asea A. Radiation-induced effects and the immune system in cancer. Front Oncol 2012;2:191.
13. Wattenberg MM, Fahim A, Ahmed MM, et al. Unlocking the combination: potentiation of radiation-induced antitumor responses with immunotherapy. Radiat Res 2014;182(2):126–138.
14. Burnette BC, Liang H, Lee Y, et al. The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity. Cancer Res 2011;71(7):2488–2496.
15. Deng L, Liang H, Xu M, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity 2014;41(5):843–852.
16. Zitvogel L, Kroemer G. Subversion of anticancer immunosurveillance by radiotherapy. Nat Immunol 2015;16(10):1005–1007.

17. R. Mole, Whole body irradiation – radiobiology or medicine?, Br J. Radiol. 26 (1953) 234–241.
18. Chi KH, Liu SJ, Li CP, et al. Combination of conformal radiotherapy and intratumoral injection of adoptive dendritic cell immunotherapy in refractory hepatoma. J Immunother 2005;28(2):129–135.
19. Shibamoto Y, Okamoto M, Kobayashi M, et al. Immune-maximizing (IMAX) therapy for cancer: Combination of dendritic cell vaccine and intensity-modulated radiation. Mol Clin Oncol 2013;1(4):649–654.
21. Gasser S, Orsulic S, Brown EJ, et al. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. Nature 2005;436(7054):1186–1190.
20. Gulley JL, Arlen PM, Bastian A, et al. Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. Clin Cancer Res 2005;11(9):3353–3362.
21. Kim J, Gulley JL. Poxviral vectors for cancer immunotherapy. Expert Opin Biol Ther. 2012; 12(4): 463–478.
22. Gulley JL, Madan RA, Tsang KY, et al. A pilot safety trial investigating a vector-based vaccine targeting carcinoembryonic antigen in combination with radiotherapy in patients with gastrointestinal malignancies metastatic to the liver. Expert Opin Biol Ther. 2011; 11:1409–18.
23. Hannan R, Zhang H, Wallecha A, et al. Combined Immunotherapy With Listeria Monocytogenes-Based PSA Vaccine and Radiation Therapy Leads to a Therapeutic Response in a Murine Model of Prostate Cancer. Cancer Immunol Immunotherapy 2010; 61 (12), 2227-38
24. Honeychurch J, Glennie MJ, Johnson PW, et al. Anti-CD40 monoclonal antibody therapy in combination with irradiation results in a CD8 T-celldependent immunity to B-cell lymphoma. Blood 2003;102(4):1449–1457.
25. Corrales L, Glickman LH, McWhirter SM, et al. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. Cell Rep 2015;11(7):1018–1030.
26. Baird JR, Friedman D, Cottam B, et al. Radiotherapy combined with novel STING-targeting oligonucleotides results in regression of established tumors. Cancer Res 2016;76(1):50–61.
27. Corrales L, McWhirter SM, Dubensky TW Jr, et al. The host STING pathway at the interface of cancer and immunity. J Clin Invest 2016;126(7):2404–2411.
28. Corrales L, Gajewski TF. Molecular pathways: targeting the stimulator of interferon genes (STING) in the immunotherapy of cancer. Clin Cancer Res 2015;21(21):4774–4779.
29. Morris ZS, Guy EI, Francis DM, et al. In situ tumor vaccination by combining local radiation and tumor-specific antibody or immunocytokine treatments. Cancer Res 2016;76(13):3929–3941.
30. Iwai Y, Hamanishi J, Chamoto K, et al. Cancer immunotherapies targeting the PD-1 signaling pathway. J Biomed Sci 2017;24(1):26-017-0329-9.
31. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74(19):5458–5468.
32. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III nonsmall-cell lung cancer. N Engl J Med 2017;377:1919–1929.
33. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015;520(7547):373–377.
34. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012;366(10):925–931.
35. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of nonsmall-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18(7):895–903.
36. Grassberger C, Ellsworth S, Willks M et al. Assessing the interactions between radiotherapy and antitumour immunity. Nature Reviews 2019;16 (12), 729-745
37. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize

CD19. Blood 2010;116(20):4099–4102.
38. Young, K. H., Baird, J. R., Savage, T. et al. Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. *PLoS ONE* 2016; 11:e0157164.
39. Qian, J. M., Yu, J. B., Kluger, H. M., et al. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* 2016; 122, 3051–3058.
40. Antonia, S. J., Villegas, A., Daniel, D., et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N. Engl. J. Med.* 2017; 377, 1919–1929.
41. Lugade, A. A., Moran, J. P., Gerber, S. A., et al. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J. Immunol.* 2005;174, 7516–7523.
42. Camphausen, K., Moses, M. A., Ménard, C., et al. Radiation abscopal antitumor effect is mediated through p53. *Cancer Res.* 2003;63, 1990–1993.
43. Dewan, M. Z., Galloway, A. E., Kawashima, N., et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin. Cancer Res.* 2009;15, 5379–5388. doi: 10.1158/1078-0432.CCR-09-0265
44. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.
45. Price JG, Idoyaga J, Salmon H, et al. CDKN1A regulates Langerhans cell survival and promotes Treg cell generation upon exposure to ionizing irradiation. Nat Immunol 2015;16(10):1060–1068.
46. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013;105(4):256–265.
47. Filatenkov A, Baker J, Mueller AM, et al. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. Clin Cancer Res 2015;21(16):3727–3739.
48. Kioi M, Vogel H, Schultz G, et al. Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. J Clin Invest 2010;120(3):694–705.
49. Kozin SV, Kamoun WS, Huang Y, et al. Recruitment of myeloid but not endothelial precursor cells facilitates tumor regrowth after local irradiation. Cancer Res 2010;70(14):5679–5685.
50. Chen Y, Ramjiawan RR, Reiberger T, et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice.Hepatology 2015;61(5):1591–1602.
51. Crittenden MR, Savage T, Cottam B, et al. The peripheral myeloid expansion driven by murine cancer progression is reversed by radiation therapy of the tumor. PLoS One 2013;8(7):e69527.
52. Ando K, Fujita H, Hosoi A, et al. Intravenous dendritic cell administration enhances suppression of lung metastasis induced by carbon-ion irradiation. J Radiat Res 2017;58(4):446–455.
53. Matsunaga A, Ueda Y, Yamada S, et al. Carbon-ion beam treatment induces systemic antitumor immunity against murine squamous cell carcinoma. Cancer 2010;116(15):3740–3748.
54. Ohkubo Y, Iwakawa M, Seino K, et al. Combining carbon ion radiotherapy and local injection of alpha-galactosylceramide-pulsed dendritic cells inhibits lung metastases in an in vivo murine model. Int J Radiat Oncol Biol Phys 2010;78(5):1524–1531.