BÖLÜM 6

MELATONİNİN KANSER TEDAVİ POTANSİYELİ VE ANTİOKSİDAN ÖZELLİKLERİ

Gülhan GÜLER AVCI [1]
Özge ULAŞ [2]

GİRİŞ

Radyoterapi (RT), kanser hastalarının yarısından fazlasının tedavisinde kritik bir rol oynamaktadır. Ancak, bu etkili tedavi yönteminin şiddetli akut ve geç yan etkileri, uygun tedaviyi sınırlayan önemli bir faktördür (1, 2). İyonlaştırıcı radyasyona (IR) maruz kalma, hücrelerde çeşitli stresleri tetikler. Bu stresler, özellikle yüksek dozlarda uygulandığında, radyasyon kaynaklı DNA, organel ve membran hasarları aracılığıyla ışınlanmış ve ışınlanmamış bölgelerde karmaşık ve kalıcı yanıtları başlatır (2). Bu yoğun hasarlar, enflamasyon, genomik instabilite, karsinojenez ve patolojik değişikliklere yol açan immün yanıtları tetiklemektedir. Bağışıklık sistemi yanıtları, radyasyonun erken ve geç yan etkilerinin çoğunda kilit bir rol oynarken, aynı zamanda tümörün radyoterapiye yanıtında, anjiyogenez ve tümör büyümesi gibi süreçlerde de önemli bir etkiye sahiptir (1, 2).

Melatonin (N-asetil-5-metoksitriptamin), güçlü bir antioksidan ve immünomodülatör ajan olarak, radyasyonun çeşitli organlarda neden olduğu toksisiteyi hafifletebilecek uygun immün düzenleyici özellikler sergilemiştir. Bu koruyucu etkiler, DNA onarım sistemi, antioksidan enzimler, immün hücreler, sitokin salgısı, transkripsiyon faktörleri ve protein kinazlar üzerindeki modülatör etkileri aracılığıyla gerçekleşir. Ayrıca, melatoninin antikanser özellikleri radyoterapinin terapötik oranını artırabilir. Meme kanseri gibi malignitelerin tedavisinde bu ajanın klinik uygulamaları umut vadeden sonuçlar göstermiştir. Melatoninin, hem

[1] Doç. Dr., Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi, Radyasyon Onkolojisi AD., drgulhanguler@hotmail.com, ORCID iD: 0000-0001-6802-2984
[2] Dr. Öğr. Üyesi, Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi, Nükleer Tıp AD., ozgeulas23@gmail.com, ORCID iD: 0000-0002-8687-5769

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Ancak, düşük biyoyararlanım, optimal dozaj belirsizliği ve ölçüm yöntemlerindeki tutarsızlıklar gibi zorlukların aşılması için daha fazla araştırmaya ve yeni farmasötik formülasyonların geliştirilmesine ihtiyaç vardır. Melatoninin kanser tedavisindeki potansiyeli tam olarak değerlendirildiğinde, onkoloji alanında önemli bir ilerleme sağlayabilir.

KAYNAKLAR

1. Najafi M, Shirazi A, Motevaseli E, et al. The melatonin immunomodulatory actions in radiotherapy. Biophys Rev. 2017;9(2):139–148.
2. Farhood B, Goradel NH, Mortezaee K, et al. Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization. Clin Transl Oncol. 2019;21:268–279.
3. Talib WH, Alsayed AR, Abuawad A, et al. Melatonin in cancer treatment: current knowledge and future opportunities. Molecules. 2021;26(9):2506.
4. Wang L, Wang C, Choi WS. Use of melatonin in cancer treatment: where are we? Int J Mol Sci. 2022;23(7):3779.
5. Härtter S, Ursing C, Morita S, et al. Orally given melatonin may serve as a probe drug for cytochrome P450 1A2 activity in vivo: a pilot study. Clin Pharmacol Ther. 2001;70:10–16.
6. Cuzzocrea S, Zingarelli B, Gilad E, et al. Protective effect of melatonin in carrageenan-induced models of local inflammation: relationship to its inhibitory effect on nitric oxide production and its peroxynitrite scavenging activity. J Pineal Res. 1997;23(2):106–116.
7. Mohseni M, Mihandoost E, Shirazi A, et al. Melatonin may play a role in modulation of bax and bcl-2 expression levels to protect rat peripheral blood lymphocytes from gamma irradiation-induced apoptosis. Mutat Res. 2012;738–739:19–27.
8. Khan S, Adhikari JS, Rizvi MA, et al. Melatonin attenuates (60)Co gamma-ray-induced hematopoietic, immunological and gastrointestinal injuries in C57BL/6 male mice. Environ Toxicol. 2017;32(2):501–518.
9. Ortiz F, Acuña-Castroviejo D, Doerrier C, et al. Melatonin blunts the mitochondrial/NLRP3 connection and protects against radiation-induced oral mucositis. J Pineal Res. 2015;58(1):34–49.
10. Aras S, Efendioğlu M, Wulamujiang A, et al. Radioprotective effect of melatonin against radiotherapy-induced cerebral cortex and cerebellum damage in rat. Int J Radiat Biol. 2021;97(3):348–355.
11. Erol FS, Topsakal C, Ozveren MF, et al. Protective effects of melatonin and vitamin E in brain damage due to gamma radiation: an experimental study. Neurosurg Rev. 2004;27:65–69.
12. Lozano A, Marruecos J, Rubió J, et al. Randomized placebo-controlled phase II trial of high-dose melatonin mucoadhesive oral gel for the prevention and treatment of oral mucositis in patients with head and neck cancer undergoing radiation therapy concurrent with systemic treatment. Clin Transl Oncol. 2021;23:1801–1810.
13. Elsabagh HH, Moussa E, Mahmoud SA, et al. Efficacy of melatonin in prevention of radiation-induced oral mucositis: a randomized clinical trial. Oral Dis. 2020;26:566–572.
14. Alonso-Gonzalez C, Gonzalez A, Martinez-Campa C, et al. Melatonin enhancement of the radiosensitivity of human breast cancer cells is associated with the modulation of proteins involved in estrogen biosynthesis. Cancer Lett. 2016;370(1):145–152.
15. Jang SS, Kim WD, Park WY. Melatonin exerts differential actions on X-ray radiation-induced apoptosis in normal mice splenocytes and Jurkat leukemia cells. J Pineal Res. 2009;47(2):147–155.
16. Zhou R, Wang R, Song J, et al. Melatonin inhibit the angiogenesis of gastric cancer by nuclear receptor. FASEB J. 2015;29(1 Suppl):639.5.
17. Lissoni P, Rovelli F, Malugani F, et al. Anti-angiogenic activity of melatonin in advanced cancer

patients. Neuroendocrinol Lett. 2001;22(1):45–48.
18. Alonso-Gonzalez C, Gonzalez A, Martinez-Campa C, et al. Melatonin sensitizes human breast cancer cells to ionizing radiation by downregulating proteins involved in double-strand DNA break repair. J Pineal Res. 2015;58(2):189–197.
19. Escames G, Guerra-Librero A, Shen Y, et al. PO-090: Oncostatic effect of melatonin in head and neck cancer: role of mitochondrial function. Radiother Oncol. 2017;122:43–44.
20. del Rio B, Garcia Pedrero JM, Martinez-Campa C, et al. Melatonin, an endogenous-specific inhibitor of estrogen receptor alpha via calmodulin. J Biol Chem. 2004;279(37):38294–38302.
21. Martinez-Campa C, Gonzalez A, Mediavilla MD, et al. Melatonin inhibits aromatase promoter expression by regulating cyclooxygenases expression and activity in breast cancer cells. Br J Cancer. 2009;101(9):1613–1619.
22. Lissoni P, Meregalli S, Nosetto L, et al. Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. Oncology. 1996;53:43–46.
23. Barni S, Lissoni P, Cazzaniga M, et al. A randomized study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. Oncology. 1995;52:243–245.
24. Seely D, Wu P, Fritz H, et al. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. Integr Cancer Ther. 2011;10:240–250.
25. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials. Cancer Chemother Pharmacol. 2012;69:1213–1220.
26. Lissoni P, Malugani F, Bukovec R, et al. Reduction of cisplatin-induced anemia by the pineal indole 5-methoxytryptamine in metastatic lung cancer patients. Neuroendocrinol Lett. 2003;24:83–86.
27. Ben-David MA, Elkayam R, Gelernter I, et al. Melatonin for prevention of breast radiation dermatitis: a phase II, prospective, double-blind randomized trial. Isr Med Assoc J. 2016;18:188–192.
28. Lissoni P, Chilelli M, Villa S, et al. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. J Pineal Res. 2003;35:12–15.
29. Seely D, Legacy M, Auer RC, et al. Adjuvant melatonin for the prevention of recurrence and mortality following lung cancer resection (AMPLCaRe): a randomized placebo controlled clinical trial. eClinicalMedicine. 2021;33:100763.
30. Lissoni P, Barni S, Cazzaniga ME, et al. Efficacy of the concomitant administration of the pineal hormone melatonin in cancer immunotherapy with low-dose IL-2 in patients with advanced solid tumors who had progressed on IL-2 alone. Oncology. 1994;51:344–347.
31. Berk L, Berkey B, Rich T, et al. Randomized phase II trial of high-dose melatonin and radiation therapy for RPA class 2 patients with brain metastases (RTOG 0119). Int J Radiat Oncol Biol Phys. 2007;68:852–857.
32. Harpsøe NG, Andersen LPH, Gögenur I, et al. Clinical pharmacokinetics of melatonin: a systematic review. Eur J Clin Pharmacol. 2015;71:901–909.
33. Ud Din F, Aman W, Ullah I, et al. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017;12:7291–7309.
34. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: a critical systematic review of clinical evidence. Complement Ther Med. 2018;42:65–81.