

## **BÖLÜM 4**

### **KONKOMİTANT KEMORADYOTERAPİ PRENSİPLERİ**

Seher BAHAR<sup>1</sup>

#### **GİRİŞ**

Onkolojik tedavilerde multidisipliner yaklaşımın önemi gün geçtikçe artmaktadır.(1) cerrahi, definitif lokal tedavi yöntemi; (2) kemoterapi definitif sistemik tedavi yöntemi (3) radyoterapi definitif lokorejyonel tedavi yöntemidir. Geçmiş zamanlarda bu yaklaşımlar ağırlıklı olarak birbiri için kullanılmış olsa da ,son yıllarda iyileştirilmiş lokal ve rejonel kontrol, kozmetik sonuçlar,organ korunması ve daha uzun genel sağkalım dahil olmak üzere daha iyi sonuçlar için bu tedavileri birleştirmeye yönelik hem klinik hem preklinik çalışmalarda artış görülmüştür. Bu tedavi modalitelerini ardışık ve eşzamanlı rejimlerde birleştiren klinik çalışmalardan kemoterapi ve radyasyon arasındaki etkileşimler hakkında çok şey öğrenilmiştir. Bununla birlikte laboratuvar araştırmaları, daha iyi sonuçlar için potansiyel olarak kullanılabilecek anahtar moleküller hedefler ve yolaklar göstermiştir. Kemoterapi ve radyasyon kombinasyonu hastalıklarda tedavi yaklaşımını değiştirmiştir. Karşılıklı veya eşzamanlı duyarlılık için radyasyon ve kemoterapinin kullanılması, bu etkileşimlerin karmaşaklığını daha da arttırır. Lösemi tedavisi için radyoterapi ve benzen tedavisi kombine edilmiştir. Bununla birlikte, muhtemelen kemoterapi ve radyasyon tedavisi etkileşiminin en iyi tarihi modeli 5-florourasil (5-FU)dir.

5-Fluorouracil; 1950'lerde, halojenli pirimidin (5-FU)'in external beam radyoterapi (EBRT) ile birleştirilmesinden sonra bu ilaç sınıfının antikanser özelliklere sahip olduğu belirlendi(1). Son elli yılda 5-FU, çeşitli gastrointestinal kanserlerin yanı sıra serviks kanseri ve baş ve boyun kanserini tedavi etmek için radyasyonla kombine edildi(2). 5-FU'nun uygulama yolu ve zamanlaması, toksisiteyi azaltmak

<sup>1</sup> Uzm. Dr. Atatürk Şehir Hastanesi, Radyasyon Onkolojisi AD., drseherbahar@gmail.com

## KAYNAKLAR

1. C Heidelberger, NK Chaudhuri, P Danneberg, et al.: Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature*. 179:663-666 1957.
2. TA Rich, RC Shepard, ST Mosley: Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol*. 22:2214-2232 2004.
3. GG Steel, MJ Peckham: Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. *Int J Radiat Oncol Biol Phys*. 5:85-91 1979.
4. JR Kouvaris, VE Kouloulias, LJ Vlahos: Amifostine: the first selective-target and broad-spectrum radioprotector. *Oncologist*. 12:738-747 2007
5. SM Bentzen, PM Harari, J Bernier: Exploitable mechanisms for combining drugs with radiation: concepts, achievements and future directions. *Nat Clin Pract Oncol*. 4:172-180 2007
6. HR Withers: Four R's of radiotherapy. *Adv Radiat Biol*. 5:241-247 1975
7. T Terasima, LJ Tolmach: Changes in x-ray sensitivity of HeLa cells during the division cycle. *Nature*. 190:1210-1211 1961
8. WK Sinclair, RA Morton: X-ray sensitivity during the cell generation cycle of cultured Chinese hamster cells. *Radiat Res*. 29:450-474 1966
9. H Choy, FF Rodriguez, S Koester, et al.: Investigation of taxol as a potential radiation sensitizer. *Cancer*. 71:3774-3778 1993
10. RB Tishler, CR Geard, EJ Hall, PB Schiff: Taxol sensitizes human astrocytoma cells to radiation. *Cancer Res*. 52:3495-3497 1992
11. RB Tishler, PB Schiff, CR Geard, EJ Hall: Taxol: a novel radiation sensitizer. *Int J Radiat Oncol Biol Phys*. 22:613-617 1992
12. CJ McGinn, TJ Kinsella: The experimental and clinical rationale for the use of S-phase-specific radiosensitizers to overcome tumor cell repopulation. *Semin Oncol*. 19:21-28 1992
13. PL Olive: Detection of hypoxia by measurement of DNA damage in individual cells from spheroids and murine tumours exposed to bioreductive drugs. I. Tirapazamine. *Br J Cancer*. 71:529-536 1995
14. L Milas, N Hunter, KA Mason, et al.: Tumor reoxygenation as a mechanism of taxol-induced enhancement of tumor radioresponse. *Acta Oncol*. 34:409-412 1995
15. P Hentosh: Induction and repair of DNA damage in gamma-irradiated human lymphoblasts: irradiation in the presence and absence of misonidazole. *Radiat Res*. 115:436-447 1988
16. S Dische: Chemical sensitizers for hypoxic cells: a decade of experience in clinical radiotherapy. *Radiother Oncol*. 3:97-115 1985
17. L Galluzzi, I Vitale, SA Aaronson, et al.: Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ*. 25:486-541 2018
18. VT DeVita, Chu E: A history of cancer chemotherapy. *Cancer Res*. 68:8643-8653 2008
19. MJ O'Connell, JA Martenson, HS Wieand, et al.: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med*. 331:502-507 1994
20. N Sawada, T Ishikawa, F Sekiguchi, et al.: X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. *Clin Cancer Res*. 5:2948-2953 1999
21. M Endo, N Shinbori, Y Fukase, et al.: Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. *Int J Cancer*. 83:127-134 1999
22. Wang X, Zhao DB, Yang L, et al.: S-1 chemotherapy and intensity-modulated radiotherapy after D1/D2 lymph node dissection in patients with node-positive gastric cancer: a phase I/II study. *Br J Cancer*. 118:338-343 2018
23. PY Chun, Feng FY, AM Scheurer, et al.: Synergistic effects of gemcitabine and gefitinib in the treatment of head and neck carcinoma. *Cancer Res*. 66:981-988 2006

24. Z Symon, M Davis, CJ McGinn, et al.: Concurrent chemoradiotherapy with gemcitabine and cisplatin for pancreatic cancer: from the laboratory to the clinic. *Int J Radiat Oncol Biol Phys.* 53:140-145 2002
25. Chen M, AM Hough, TS Lawrence: The role of p53 in gemcitabine-mediated cytotoxicity and radiosensitization. *Cancer Chemother Pharmacol.* 45:369-374 2000
26. TS Lawrence, A Eisbruch, CJ McGinn, et al.: Radiosensitization by gemcitabine. *Oncology (Wiliston Park).* 13:55-60 1999
27. CJ McGinn, MM Zalupski, I Shureiqi, et al.: Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 19:4202-4208 2001
28. N Adhikari, A Biswas, A Gogia, et al.: A prospective phase II trial of response adapted whole brain radiotherapy after high dose methotrexate based chemotherapy in patients with newly diagnosed primary central nervous system lymphoma-analysis of acute toxicity profile and early clinical outcome. *J Neurooncol.* 139:153-166 2018
29. Wang Y, Liu S, Wei X, et al.: Non-small cell lung cancer leptomeningeal metastases treated with intrathecal therapy plus osimertinib and temozolamide and whole-brain radiation therapy: a case report. *Onco Targets Ther.* 11:4733-4738 2018
30. Wang JC: DNA topoisomerasers. *Annu Rev Biochem.* 65:635-692 1996
31. BA Teicher, Chen V, C Shih, et al.: Treatment regimens including the multitargeted antifolate LY231514 in human tumor xenografts. *Clin Cancer Res.* 6:1016-1023 2000
32. M Bischof, P Huber, C Stoffregen, et al.: Radiosensitization by pemetrexed of human colon carcinoma cells in different cell cycle phases. *Int J Radiat Oncol Biol Phys.* 57:289-292 2003
33. M Bischof, KJ Weber, J Blatter, et al.: Interaction of pemetrexed disodium (ALIMTA, multitargeted antifolate) and irradiation in vitro. *Int J Radiat Oncol Biol Phys.* 52:1381-1388 2002
34. FE Adair, HJ Bagg: Experimental and clinical studies on the treatment of cancer by dichlorethylsulphide (mustard gas). *Ann Surg.* 93:190-199 1931
35. MC Heinrich, ME Hoatlin, AJ Zigler, et al.: DNA cross-linker-induced G2/M arrest in group C Fanconi anemia lymphoblasts reflects normal checkpoint function. *Blood.* 91:275-287 1998
36. K Sugiyama, M Shimizu, T Akiyama, et al.: UCN-01 selectively enhances mitomycin C cytotoxicity in p53 defective cells which is mediated through S and/or G(2) checkpoint abrogation. *Int J Cancer.* 85:703-709 2000
37. M De Ridder, G Van Esch, B Engels, et al.: Hypoxic tumor cell radiosensitization: role of the iNOS/NO pathway. *Bull Cancer.* 95:282-291 2008
38. JA Ajani, KA Winter, LL Gunderson, et al.: Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA.* 299:1914-1921 2008
39. ND Nigro, VK Vaitkevicius, B Considine Jr: Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum.* 17:354-356 1974
40. Amarasingh S, Macleod MR, Whittle IR. What is the translational efficacy of chemotherapeutic drug research in neuro-oncology? A systematic review and meta-analysis of the efficacy of BCNU and CCNU in animal models of glioma. *J Neurooncol.* 2009;91:117-125.
41. Amarasingh S, Macleod MR, Whittle IR. What is the translational efficacy of chemotherapeutic drug research in neuro-oncology? A systematic review and meta-analysis of the efficacy of BCNU and CCNU in animal models of glioma. *J Neurooncol.* 2009;91:117-125.
42. Soloway MS, Morris CR, Suderth B. Radiation therapy and cis-diammine-dichloroplatinum (II) in transplantable and primary murine bladder cancer. *Int J Radiat Oncol Biol Phys.* 1979;5:1355-1360
43. Amorino GP, Freeman ML, Carbone DP, et al. Radiopotentiation by the oral platinum agent, JM216: role of repair inhibition. *Int J Radiat Oncol Biol Phys.* 1999;44:399-405.
44. Behmand B, Marignier JL, Mostafavi M, et al. Radiosensitization of DNA by cisplatin adducts results from an increase in the rate constant for the reaction with hydrated electrons and formation of Pt(I). *J Phys Chem B.* 2015;119:9496-9500.

45. Wilson GD, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. *Semin Radiat Oncol.* 2006;16:2–9
46. Ryu S, Gabel M, Khil MS, et al. Estramustine: a novel radiation enhancer in human carcinoma cells. *Int J Radiat Oncol Biol Phys.* 1994;30:99–104.
47. Perez EA. Microtubule inhibitors: differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. *Mol Cancer Ther.* 2009;8:2086–2095.