BÖLÜM 4

Gastrointestinal Sistem Kanserlerinin Tedavisinde İlaç Direncinin Moleküler Mekanizmaları

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Giriş

Tüm dünyada kardiyovasküler hastalıklardan sonra en sık görülen ve yaşam süresini azaltan hastalık kanserdir. Erkeklerde akciğer ve prostat kadınlarda ise meme kanserinden sonra görülen kansere bağlı ölümler sıklıkla özofagus, mide, kolorektal, karaciğer ve pankreas dahil olmak üzere gastrointestinal kanaldan kaynaklanan kanserler nedeni ile olmaktadır (1, 2). Cerrahi, radyasyon tedavisi, kemoterapi, kombinasyon tedavisi ve lazer tedavisi gibi yaygın kanser tedavilerine ek olarak, biyoloji ve moleküler genetiğin daha iyi anlaşılmasına dayanan seçici tedaviler tümör progresyonunu önlemek için umut verici görünmektedir (3).

Gastrointestinal kanserler için de temel tedavi stratejisi cerrahi rezeksiyon olmakla birlikte, rezeke edilemeyen veya tekrarlayan hastalığı olan hastalarda, radyoterapi ve kemoterapi öncelikli tedavi seçenekleri olarak karşımıza çıkmaktadır (2). Ayrıca hedefe yönelik tedaviler ve immünoterapi, gastrointestinal kanser hastalarının sağ kalımını arttırmak için yakın zamanda geliştirilmiş alternatiflerdir (3). Ancak ileri evre GİS kanserli hastaların çoğu söz konusu tedavi yöntemlerine dirençlidir ve bu nedenle hayatta kalma oranları düşüktür. Günümüzde tedavi yöntemlerinde sağlanabilen ilerlemelere rağmen kanser tedavisinde yine de umut vadeden bir seçenek olan kemoterapiye karşı oluşan direncin birden çok moleküler temele dayandığını söylemek mümkündür (4).

Tümörlerde ilaç rezistansı, intrensek (primer) veya adaptif (sekonder) nedenlerle olabilir ve aşağıdaki mekanizmalardan biri veya birkaçı tarafından oluşturulabilir;

1. Hücre içi ilaçların etkili konsantrasyonunun azalması,

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Ancak cerrahi tedavi görme şansı olmayan hastalar için kapsamlı tedavinin nihai hedefi, sağkalımı uzatmak ve yaşam kalitesini yükseltmektir. Yeni kemoterapi ilaçlarının geliştirilmesi, hedefe yönelik ilaçlar, immünoterapilerin geliştirilmesi sayesinde daha kapsamlı ve kişiselleştirilmiş bir teşhis ve tedavi stratejisi uygulayarak hastalara daha iyi klinik fayda sağlanabilecektir.

Kemoterapide direnç sorununu çözmek her ne kadar ulaşılamaz bir hedef gibi görünüyor olsa da kanser araştırmacılarının moleküler satranç oynamayı öğrenmesi ve belki de bir sonraki hamleye hazırlanabileceği çalışmaların hızla devam etmesi ile üstesinden gelinebilir hal alacak ve daha yüz güldürücü tedavi olanakları ortaya konacaktır.

Kaynaklar

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021:71:209-249. https://doi.org/10.3322/caac.21660
2. Ham I-H, Lee D, Hur H. Cancer-Associated Fibroblast-Induced Resistance to Chemotherapy and Radiotherapy in Gastrointestinal Cancers. Cancers (Basel). 2021:13(5):1172. https://doi.org/10.3390/cancers13051172
3. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol. 2005;205(2):275-292. doi: 10.1002/path.1706.
4. Fatima, B., Jamil, M., Hussain, D., et al. (2021) Drug Resistance in Cancer. Sarfraz Ahmed, Suvash Chandra Ojha, Muhammad Najam-ul-Haq, Muhammad Younus, Muhammad Zaffar Hashmi. (Ed) 367-387. Switzerland: Springer Nature.
5. Ruan T, Liu W, Tao K, et. al. A Review of Research Progress in Multidrug-Resistance Mechanisms in Gastric Cancer. Onco Targets Ther. 2020;13:1797-1807. doi:10.2147/OTT.S239336
6. Lo HW, Ali-Osman F. Genetic polymorphism and function of glutathione S-transferases in tumor drug resistance. Curr Opin Pharmacol. 2007;7(4):367–374. doi:10.1016/j.coph.2007.06.009.
7. Peters WH, Wormskamp NG, Thies E. Expression of glutathione S-transferases in normal gastric mucosa and in gastric tumors. Carcinogenesis. 1990;11(9):1593–1596. doi:10.1093/carcin/ 11.9.1593
8. Joncourt F, Buser K, Altermatt H, et al. Multiple Drug Resistance Parameter Expression in Ovarian Cancer. Gynecol Oncol. 1998;70:176-182.
9. De Bruin WC, Wagenmans MJ, Peters WH. Expression of glutathione S-transferase alpha, P1-1 and T1-1 in the human gastrointestinal tract. JPN J Cancer Res. 2000;91(3):310-316. doi: 10.1111/j.1349-7006.2000.tb00946.x.
10. Goto S, Iida T, Cho S, et al. Overexpression of glutathione S-transferase pi enhances the adduct formation of cisplatin with glutathione in human cancer cells. Free Radic Res. 1999;31(6):549-558. doi: 10.1080/10715769900301121.
11. Geng M, Wang L, Chen X, et al. The association between chemosensitivity and Pgp, GST-pi and Topo II expression in gastric cancer. Diagnos Pathol. 2013;8:198-193. doi: 10.1186/1746-1596-8-198.
12. Okuyama T, Maehara Y, Endo K, et al. Expression of glutathione Stransferase-pi and sensitivity of human gastric cancer cells to cisplatin. Cancer, 1994;74(4):1230-1236. doi: 10.1002/1097-0142(19940815)74:4<1230::aid-cncr2820740409>3.0.co;2-0.
13. Cui H, Zhang AJ, Chen M, et al. ABC transporter inhibitors in reversing multidrug resistance to chemotherapy. Curr Drug Targets. 2015;16(12):1356–1371. doi:10.2174/1389450116666150330113506
14. Monden N, Abe S, Hishikawa Y, et al. The role of P-glycoprotein in human gastric cancer xenografts in response to chemotherapy. Int J Surg Investig. 1999;1(1):3-10.
15. Rocco A, Compare D, Liguori E, et al. MDR1-P-glycoprotein behaves as an oncofetal protein that promotes cell survival in gastric cancer cells. Lab Invest. 2012;92(10):1407-1418. doi: 10.1038/labinvest.2012.100
16. de Oliveira J, Felipe AV, Neto RA, et al. Association between ABCB1 immunohistochemical expression and overall survival in gastric cancer patients. Asian Pac J Cancer Prev. 2014;15(16):6935–6938. doi:10.7314/ APJCP.2014.15.16.6935.
17. Chung HC, Gong SJ, Yoo NC, et al. P-glycoprotein as an intermediate end point of drug resistance to neoadjuvant chemotherapy in locally advanced gastric cancer. Yonsei Med J. 1996;37(6):397-404. doi:10.3349/ymj.1996.37.6.397.
18. Zhu CY, Lv YP, Yan DF, et al. Knockdown of MDR1 increases the sensitivity to adriamycin in drug resistant gastric cancer cells. Asian Pac J Cancer Prev. 2013;14(11):6757-6760. doi: 10.7314/apjcp.2013.14.11.6757.
19. Tanaka M, Kataoka H, Yano S, et al. Anti-cancer effects of newly developed chemotherapeutic agent, glycoconjugated palladium (II) complex, against cisplatin-resistant gastric cancer cells. BMC Cancer. 2013;13:237-246. doi: 10.1186/1471-2407-13-237.
20. Obuchi W, Ohtsuki S, Uchida Y, et al. Identification of transporters associated with Etoposide sensitivity of stomach Cancer Cell lines and methotrexate sensitivity of breast Cancer Cell lines by quantitative targeted

absolute proteomics. Mol Pharmacol. 2013;83(2):490-500. doi: 10.1124/mol.112.081083
21. Furmanski BD, Hu S, Fujita K, et al. Contribution of ABCC4-mediated gastric transport to the absorption and efficacy of dasatinib. Clin Cancer Res. 2013;19:(16):4359-4370. doi: 10.1158/1078-0432.CCR-13-0980.
22. Marin JJ, Romero MR, Martinez-Becerra P, et al. Overview of the molecular bases of resistance to chemotherapy in liver and gastrointestinal tumours. Curr Mol Med. 2009;9(9):1108-1129. Doi: 10.2174/156652409789839125.
23. Kim R, Ohi Y, Inoue H, Toge T. Expression and relationship between topoisomerase I and II alpha genes in tumor and normal tissues in esophageal, gastric and colon cancers. Anticancer Res. 1999;19(6b):5393-5398. PMID: 10697567.
24. Wang G, Huang H, Gao J, et al. Tissue microarray analysis of topoisomerase II alpha protein in gastric adenocarcinomas: histogenetic and prognostic implications. Cancer Genomics Proteomics. 2011;8(3):127-133. PMID: 21518818.
25. Yu P, Du Y, Yang L, et al. Significance of multidrug resistance gene-related proteins in the postoperative chemotherapy of gastric cancer. Int J Clin Exp Pathol. 2014;7(11):7945–7950. PMID: 25550836.
26. Son YS, Suh JM, Ahn SH, et al. Reduced activity of topoisomerase II in an Adriamycin-resistant human stomach-adenocarcinoma cell line. Cancer Chemother Pharmacol. 1998;41(5):353-360. doi:10.1007/s002800050751
27. Zugazagoitia J, Guedes C, Ponce S, et al. Current challenges in cancer treatment. Clin Ther. 2016;38(7):1551-1566. doi:10.1016/j.clinthera.2016.03.026
28. Zheng S, Huang KE, Pan YL, et al. KIT and BRAF heterogeneous mutations in gastrointestinal stromal tumors after secondary imatinib resistance. Gastric Cancer. 2015;18(4):796-802. doi:10.1007/s10120-014-0414-7.
29. Serrano C, Wang Y, Marino-Enriquez A, et al. KRAS and KIT gatekeeper mutations confer polyclonal primary imatinib resistance in gi stromal tumors: relevance of concomitant phosphatidylinositol 3-kinase/AKT dysregulation. J Clin Oncol. 2015;33(22):93-96. doi:10.1200/JCO.2013.48.7488.
30. Uchida K, Hayashi K, Kuramochi H, et al. Changes in intratumoral thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) mRNA expression in colorectal and gastric cancer during continuous tegafur infusion. Int J Oncol. 2001;19:(2):341-346. doi: 10.3892/ijo.19.2.341.
31. Chu E, Voeller DM, Jones KL, et al. Identification of a thymidylate synthase ribonucleoprotein complex in human colon cancer cells. Mol Cell Biol. 1994;14:207-213. doi: 10.1128/mcb.14.1.207-213.1994.
32. Hofler H, Langer R, Ott K, et al. Prediction of response to neoadjuvant chemotherapy in carcinomas of the upper gastrointestinal tract. Adv Exp Med Biol. 2006;587:115-120. doi: 10.1007/978-1-4020-5133-3_11.
33. Chen JS, Chao Y, Bang YJ, et al. A phase I/II and pharmacogenomic study of pemetrexed and cisplatin in patients with unresectable, advanced gastric carcinoma. Anticancer Drugs. 2010;21(8):777-784. doi: 10.1097/CAD.0b013e32833cfbca.
34. Ji M, Xu B, Jiang JT, et al. Relationship between glutathione Stransferase P1 (GSTP1), X-ray repair cross complementing group 1 (XRCC1) and 5,10-methylenetetrahydrofolate reductase (5,10-MTHFR) gene polymorphisms and response to chemotherapy in advanced gastric cancer. Onkologie. 2013;36(6):335-340. doi: 10.1159/000351260.
35. Borst P, Evers R, Kool M, et al. A family of drug transporters: The multidrug resistance-associated proteins. J Natl Cancer Inst. 2000;92(16):1295-302. doi: 10.1093/jnci/92.16.1295.
36. Sanchez-Olea R, Calera MR, Degterev A. Molecular pathways involved in cell death after chemically induced DNA damage. Exs. 2009;99:209-230. doi:10.1007/978-3-7643-8336-7_8
37. Boland CR. Roles of the DNA mismatch repair genes in colorectal tumorigenesis. Int J Cancer. 1996;69(1):47-49. doi:10.1002/(ISSN)1097-0215
38. de Pagter MS, Kloosterman WP. The Diverse Effects of Complex Chromosome Rearrangements and Chromothripsis in Cancer Development. Recent Results Cancer Res. 2015;200:165-93. doi: 10.1007/978-3-319-20291-4_8. PMID: 26376877
39. Simonelli V, Leuzzi G, Basile G, et al. Crosstalk between mismatch repair and base excision repair in human gastric cancer. Oncotarget. 2017;8(49):84827–84840. doi:10.18632/oncotarget. v8i49
40. Beach LR, Palmiter RD. Amplification of the metallothionein-I gene in cadmium-resistant mouse cells. Proc Natl Acad Sci USA. 1981;78(4):2110-2114. doi: 10.1073/pnas.78.4.2110
41. Mansoori B, Mohammadi A, Davudian S, et al. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 2017;7(3):339-348. doi:10.15171/apb.2017.041
42. Mizushima N, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. Annu Rev Cell Dev Biol. 2011;27:107–132. doi:10.1146/annurev-cellbio-092910-154005
43. Yoshida GJ. Therapeutic strategies of drug repositioning targeting autophagy to induce cancer cell death: from pathophysiology to treatment. J Hematol Oncol. 2017;10(1):67. doi:10.1186/s13045-017-0436-9
44. White E, DiPaola RS. The double-edged sword of autophagy modulation in cancer. Clin Cancer Res. 2009;15(17):5308–5316. doi:10.1158/1078-0432.CCR-07-5023
45. Kondo Y, Kanzawa T, Sawaya R, et al. The role of autophagy in cancer development and response to therapy. Nat Rev Cancer. 2005;5(9):726-734. doi:10.1038/nrc1692
46. Amaravadi RK, Lippincott-Schwartz J, Yin X-M, et al. Principles and current strategies for targeting autophagy for cancer treatment. Clin Cancer Res. 2011;17(4):654-666. doi:10.1158/1078-0432.CCR-10-2634

47. Cao Y, Luo Y, Zou J, et al. Autophagy and its role in gastric cancer. Clin Chim Acta. 2019;489:10–20. doi:10.1016/j. cca.2018.11.028
48. Qian H-R, Yang Y. Functional role of autophagy in gastric cancer. Oncotarget. 2016;7(14):17641-17651. doi:10.18632/oncotarget.v7i14
49. Al-Akra L, Bae D-H, Leck LYW, et al. The biochemical and molecular mechanisms involved in the role of tumor micro-environment stress in development of drug resistance. Biochim Biophys Acta Gen Subj. 2019;1863(9):1390-1397. doi:10.1016/j.bbagen.2019.06.007
50. Li ZW, Dalton WS. Tumor microenvironment and drug resistance in hematologic malignancies. Blood Rev. 2006;20(6):333-342. doi: 10.1016/j.blre.2005.08.003
51. Nakamura K, Mori M, Enjoji M. Distribution of basement membrane antigens in clinical gastric adenocarcinomas: an immunohistochemical study. J Clin Pathol. 1987;40(12):1418-1423. doi:10.1136/jcp.40.12.1418
52. Sun L, Liu L, Liu X, et al. Gastric cancer cell adhesion to laminin enhances acquired chemotherapeutic drug resistance mediated by MGr1-Ag/37LRP. Oncol Rep. 2014;32(1):105–114. doi:10.3892/ or.2014.3184
53. Sun L, Liu L, Liu X, et al. MGr1-Ag/37LRP induces cell adhesion-mediated drug resistance through FAK/PI3K and MAPK pathway in gastric cancer. Cancer Sci. 2014;105(6):651-659. doi:10.1111/cas.12414
54. Ock CY, Nam AR, Bang JH, et al. Signature of cytokines and angiogenic factors (CAFs) defines a clinically distinct subgroup of gastric cancer. Gastric Cancer. 2017;20(1):164-174. doi:10.1007/s10120-015-0583-z
55. Yang Z, Guo L, Liu D, et al. Acquisition of resistance to trastuzumab in gastric cancer cells is associated with activation of IL-6/ STAT3/Jagged-1/Notch positive feedback loop. Oncotarget. 2015;6(7):5072-5087. doi:10.18632/oncotarget.3241
56. Ye XL, Zhao YR, Weng GB, et al. IL-33-induced JNK pathway activation confers gastric cancer chemotherapy resistance. Oncol Rep. 2015;33(6):2746–2752. doi:10.3892/or.2015.3898
57. Mao Z, Bian G, Sheng W, et al. Adenovirusmediated IL-24 expression enhances the chemosensitivity of multidrug-resistantgastric cancer cells to cisplatin. Oncol Rep. 2013;30(5):2288-2296. doi:10.3892/or.2013.2695
58. Huang T, Song C, Zheng L, Xia L, Li Y, Zhou Y. The roles of extracellular vesicles in gastric cancer development, microenvironment, anti-cancer drug resistance, and therapy. Mol Cancer. 2019;18(1):62. doi:10.1186/s12943-019-0967-5
59. Schorey JS, Bhatnagar S. Exosome function: from tumor immunology to pathogen biology. Traffic. 2008;9(6):871-881. doi:10.1111/j.1600-0854.2008.00734.x
60. Skog J, Wurdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol. 2008;10(12):1470-1476. doi:10.1038/ncb1800
61. Wang M, Qiu R, Yu S, et al. Paclitaxelresistant gastric cancer MGC803 cells promote epithelialtomesenchymal transition and chemoresistance in paclitaxelsensitive cells via exosomal delivery of miR1555p. Int J Oncol. 2019;54(1):326–338. doi:10.3892/ijo.2018.4601
62. Ji R, Zhang B, Zhang X, et al. Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. Cell Cycle. 2015;14(15):2473–2483. doi:10.1080/15384101.2015.1005530
63. Tsang WP, Kwok TT. Riboregulator H19 induction of MDR1-associated drug resistance in human hepatocellular carcinoma cells. Oncogene. 2007; 26:4877-4881. doi:10.1038/sj.onc.1210266.
64. Wang Y, Zhang DX, Wu KC, et al. Long noncoding RNA MRUL promotes ABCB1 expression in multidrug-resistant gastric cancer cell sublines. Mol Cell Biol. 2014;34:3182-3193. doi:10.1128/MCB.01580-13
65. Ikemura K, Iwamoto T, Okuda M. MicroRNAs as regulators of drug transporters, drug-metabolizing enzymes, and tight junctions: implication for intestinal barrier function. Pharmacol Ther. 2014;143:217–224. doi:10.1016/j.pharmthera.2014.03.002
66. Pullen TJ, Xavier GD, Kelsey G, et al. miR-29a and miR-29b contribute to pancreatic beta-cell-specific silencing of monocarboxylate transporter 1 (Mct1). Mol Cell Biol. 2011:31:3182-3194. doi:10.1128/MCB.01433-10
67. Dalmasso G, Hang TTN, Yan YT et al. MicroRNA-92b regulates expression of the oligopeptide transporter PepT1 in intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2011;300:G52-59. doi:10.1152/ajpgi.00394.2010
68. Zhang JX, Xu Y, Gao Y, et al. Decreased expression of miR-939 contributes to chemoresistance and metastasis of gastric cancer via dysregulation of SLC34A2 and Raf/MEK/ERK pathway. Mol Cancer. 2017;16:18-33. doi:10.1186/s12943-017-0586-y
69. Pan YZ, Gao WQ, Yu AM. MicroRNAs regulate CYP3A4 expression via direct and indirect targeting. Drug Metab Dispos. 2009;37:2112–2117. doi:10.1124/dmd.109.027680