

NÜKS VEYA METASTATİK OVER KANSERİNDE HEDEFE YÖNELİK TEDAVİLER

Büşra NİĞDELİOĞLU

GİRİŞ

Tüm primer over kanserlerin yaklaşık% 90'ı epitelyal karsinomlardır [1]. Epitelial over kanseri (EOK) birçok kemoterapötik ajana duyarlıdır ve mevcut standart tedavi

- Sitoredüktif cerrahi,
- Ardından sisplatin veya karboplatin gibi **platin** bileşikleri ve paklitaksel gibi bir **taksan** ajan ile kemoterapi uygulanmasıdır[2].

Bununla birlikte ileri EOC'li hastaların yüksek bir yüzdesi sonunda 3 yıl içinde tekrarlayan hastalık geliştirir ve evre III veya IV hastalığı ile başvuran hastaların sadece% 10-30'unda ilk tanıdan 5 yıl sonra hayatı kalır [2-3]. Bu düşük sağkalım oranı kemoterapi direncinin gelişmesinden kaynaklanmaktadır. Platin dirençli hastalarda tedavi seçenekleri , topotekan, gemitinabin ve pegile lipozomal doksorubisin gibi platin ve taksan olmayan kemoterapötiklerle sınırlıdır [4]. Bu nedenle, platin dirençli hastalık için alternatif tedavi seçenekleri sürekli araştırılmaktadır.

Klinik olarak, günümüzde en yaygın kullanılan ilaç sınıfları antianjiyogenetik ve poli (ADP-riboz) polimeraz inhibitörleridir. Bununla birlikte, geliştirme aşamasında değişen aşamalardaki bazı ilaçlar çok çeşitli biyokimyasal yolları hedef alır. Bu ilaçların aktivitesi ve yanıt oranları çok değişkendir. Kombinasyon ilaç tedavisi ve uygun hasta seçimi hakkında sorular devam ediyor.

ANJİYOGENEZ İNHİBİTÖRLERİ

Anjiyogenez normal over fizyolojisinde ve EOK patogenezinde, asit oluşumunda progresyonda ve metastatik yayılımda temel bir rol oynar. Katı tümörler, hipoksik ortamlarda büyümeye ve hayatı kalmak için neovaskülarizasyon oluşturur. Anji-

L1'in negatif olsa da tedaviden fayda sağladığı görülmüştür. Bununla birlikte, PD-L1 ekspresyonunu belirlemek için kesin bir test yoktur ve PD-L1 pozitif durumu için kesin bir referans henüz oluşturulmamıştır.

Over kanseri, tedavi seçenekleri birkaç on yıl boyunca iyileşmesine rağmen, klinisyenler için en zor kanser olmaya devam etmektedir. Son zamanlarda, over kanseri tedavisinde en büyük gelişme bevacizumab ve PARP inhibitör tedavilerinden kaynaklanmaktadır. Over kanseri, hedeflenebilir bir tümör olmasına rağmen, biyolojisi benzersiz ve oldukça heterojendir. Yeni geliştirilen ilaçlar, özellikle PD-1 / PD-L1 antikoru, umut verici sonuçlar vermiştir. Moleküler mekanizmları daha tam olarak anlamak ve direnci yenmek için hedef kombinasyon tedavileri geliştirmek için bu araştırmaların asgari toksisite ile daha fazla araştırılmasına ihtiyaç vardır. Yakın gelecekte moleküler özelliklere dayalı daha özel tedaviler beklenmektedir.

REFERANSLAR

1. Prat J. New insights into ovarian cancer pathology. *Annals of Oncology*. 2012;23(suppl 10): x111-x117. DOI: 10.1093/annonc/mds300
2. Cannistra SA. Cancer of the ovary. *The New England Journal of Medicine*. 2004;351:2519- 2529. DOI: 10.1056/NEJMra041842 [4] Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. *Seminars in Oncology*. 2006;33(suppl 6):12-16. DOI: <https://doi.org/10.1053/j.seminoncol.2006.03.012>
3. Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. *Seminars in Oncology*. 2006;33(suppl 6):12-16. DOI: <https://doi.org/10.1053/j.seminoncol.2006.03.012>
4. Karabulut B, Sezgin C, Terek M, et al. Topotecan in platinum-resistant epithelial ovarian cancer. *Chemotherapy*. 2005;51:347-351. DOI: 10.1159/000088959
5. Spannuth WA, Nick AM, Jennings NB, Armaiz-Pena GN, Mangala LS, Danes CG, Lin YG, Merritt WM, Thaker PH, Kamat AA, Han LY, Tonra JR, Coleman RL, Ellis LM, Sood AK. Functional significance of VEGFR-2 on ovarian cancer cells. *International Journal of Cancer*. 2009;124(5):1045-1053. DOI: 10.1002/ijc.24028
6. Chase DM, Chaplin DJ, Monk BJ. The development and use of vascular targeted therapy in ovarian cancer. *Gynecologic Oncology* 2017;145:393-406. DOI: <http://dx.doi.org/10.1016/j.ygyno.2017.01.031>
7. Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2015; 139:10.
8. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; 30:2039.
9. Aghajanian C, Goff B, Nycum LR, et al. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. *Gynecol Oncol* 2014; 133:105.
10. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017; 18:779.

11. Bevacizumab for intravenous infusion. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125085s-317lbl.pdf (Accessed on August 20, 2019).
12. Dinkic C et al. Pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant, recurrent, pre-treated ovarian cancer—Results of the PACOVAR-trial. *Gynecologic Oncology*. 2017;146(2):279–284. DOI: 10.1016/j.ygyno.2017.05.013
13. Kumaran GC, Jayson GC, Clamp AR. Antiangiogenic drugs in ovarian cancer. *British Journal of Cancer*. 2009;100(1):1-7. DOI: 10.1038/sj.bjc.6604767
14. Tew WP, Colombo N, Ray-Coquard I, del Campo JM, Oza A, Pereira D, Mammoliti S, et al. Intravenous afibbercept in patients with platinum-resistant, advanced ovarian cancer: Results of a randomized, double-blind, phase II, parallel-arm study. *Cancer*. 2014;120:335–343. DOI: 10.1002/cncr.28406
15. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 387:1066.
16. Norrie J. ICON-6: the danger of changing study design midstream. *Lancet* 2016; 387:1031.
17. Niraparib capsules, for oral use. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf (Accessed on August 15, 2019).
18. Olaparib tablets, for oral use. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208558s000lbl.pdf (Accessed on August 15, 2019).
19. Rucaparib tablets, for oral use. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209115s003lbl.pdf (Accessed on August 15, 2019).
20. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016; 375:2154.
21. Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2018; 19:1117.
22. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; 366:1382.
23. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer* 2018; 119:1075.
24. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390:1949.
25. Dizon DS. PARP inhibitors for targeted treatment in ovarian cancer. *Lancet* 2017; 390:1929.
26. Serpe L, Gallicchio M, Canaparo R, Dosio F. Targeted treatment of folate receptorpositive platinum-resistant ovarian cancer and companion diagnostics, with specific focus on vintafolide and etarfolatide. *Pharmacogenomics and Personalized Medicine*. 2014;7:31-42. DOI: 10.2147/PGPM.S58374
27. Morphotek—An efficacy and safety study of MORAb-003 in platinum-resistant or refractory relapsed ovarian cancer (FAR-122). Available from: <http://clinicaltrials.gov/show/NCT00738699>. NLM identifier: NCT00738699. [Accessed: September 1, 2017]
28. Dosio F, Milla P, Cattell L. EC-145, a folate-targeted vinca alkaloid conjugate for the potential treatment of folate receptor-expressing cancers. *Current Opinion in Investigational Drugs*. 2010;11(12):1424-1433
29. Naumann W, Coleman R, Robert A, Burger R, Sausville E, Kutarska E, Ghamande S, Gabrail N, DePasquale S, et al. PRECEDENT: A randomized phase II trial comparing vintafolide (EC145)

- and pegylated liposomal doxorubicin (PLD) in combination versus PLD alone in patients with platinum-resistant ovarian cancer. *Journal of Clinical Oncology*. 2013;31(35):4400-4406. DOI: 10.1200/JCO.2013.49.7685
- 30. Hudson LG, Zeineldin R, Silberberg M, Stack MS. Activated epidermal growth factor receptor in ovarian cancer. *Cancer Treatment and Research*. 2009;149:203-226. DOI: 10.1007/978-0-387-98094-2_10
 - 31. Siwak DR, Carey M, Hennessy BT, et al. Targeting the epidermal growth factor receptor in epithelial ovarian cancer: Current knowledge and future challenges. *Journal of Oncology*. 2010;2010. DOI: 10.1155/2010/568938
 - 32. Kurzeder C, Bover I, Marne F, et al. Double-blind, placebo-controlled, randomized phase III trial evaluating pertuzumab combined with chemotherapy for low tumorhuman epidermal growth factor receptor 3 mRNA-expressing platinum-resistant ovarian cancer (PENELOPE). *Journal of Clinical Oncology*. 2016;34:2516-2525. DOI: 10.1200/JCO.2015.66.0787
 - 33. Teplinsky E, Muggia F. EGFR and HER2: Is there a role in ovarian cancer? *Translational Cancer Research*. 2015;4(1):107-117. DOI: 10.3978/j.issn.2218-676X.2015.01.01
 - 34. Yunusova NV, Villert AB, Spirina LV, Frolova AE, Kolomiets LA, Kondakova IV. Insulinlike growth factors and their binding proteins in tumors and ascites of ovarian cancer patients: Association with response to Neoadjuvant chemotherapy. *Asian Pacific Journal of Cancer Prevention*. 2016;17(12):5315-5320. DOI: <http://doi.org/10.22034/APJCP.2016.17.12.5315>
 - 35. Harb WA, Sessa C, Hirte HW, Kaye SB, Banerjee SN, Christinat A, et al. Final results of a phase I study evaluating the combination of linsitinib, a dual inhibitor of insulinlike growth factor-1 receptor (IGF-1R), and insulin receptor (IR) with weekly paclitaxel (PAC) in patients (Pts) with advanced solid tumors. *Journal of Clinical Oncology*. 2013;31(15_suppl):e13502-e13502. DOI: 10.1200/jco.2013.31.15_suppl.e13502
 - 36. Schaller MD, Borgman CA, Cobb BS, Vines RR, Reynolds AB, Parsons JT. pp125FAK a structurally distinctive protein-tyrosine kinase associated with focal adhesions. *Proceedings of the National Academy of Sciences of the United States of America*. 1992;89:5192-5196
 - 37. Hungerford JE, Compton MT, Matter ML, Hoffstrom BG, Otey CA. Inhibition of pp125FAK in cultured fibroblasts results in apoptosis. *The Journal of Cell Biology*. 1996;135:1383-1390
 - 38. Frisch SM, Vuori K, Ruoslahti E, Chan-Hui PY. Control of adhesion-dependent cell survival by focal adhesion kinase. *The Journal of Cell Biology*. 1996;134:793-799
 - 39. Sood AK, Coffin JE, Schneider GB, Fletcher MS, DeYoung BR, Gruman LM, Gershenson DM, Schaller MD, Hendrix MJC. Biological significance of focal adhesion kinase in ovarian cancer: Role in migration and invasion. *American Journal of Pathology*. 2004;165:1087- 1095. DOI: 10.1016/S0002-9440(10)63370-6
 - 40. Bonome T, Lee JY, Park DC, et al. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. *Cancer Research*. 2005;65:10602-10612. DOI: 10.1158/0008-5472.CAN-05-2240
 - 41. Ward KK, Tancioni I, Lawson C, Miller NLG, Jean C, Chen XL, et al. Inhibition of focal adhesion kinase (FAK) activity prevents anchorage-independent ovarian carcinoma cell growth and tumor progression. *Clinical & Experimental Metastasis*. 2013;30(5):579-594. DOI: <http://doi.org/10.1007/s10585-012-9562-5>
 - 42. Reboe M, Levy A, Dhadyuthapani S, Rathinavelu A. Y15 enhances the cytotoxic profile of cisplatin, paclitaxel and vitamin E in platinum resistant ovarian cancer cells. *The Faseb Journal*. 2015;29:785.1
 - 43. Vaughan S, Coward JI, Bast RC Jr, et al. Rethinking ovarian cancer: Recommendations for improving outcomes. *Nature Reviews. Cancer*. 2011;11(10):719-725. DOI: 10.1038/nrc3144
 - 44. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005;434(7035):917-921. DOI: 10.1038/nature03445
 - 45. Chen Y-L, Chang M-C, Huang C-Y, et al. Serous ovarian carcinoma patients with high alpha-folate receptor had reducing survival and cytotoxic chemo-response. *Molecular Oncology*. 2012;6(3):360-369. DOI: 10.1016/j.molonc.2011.11.010