

Non-Metastatik Kastrasyona Dirençli Prostat Kanseri Tedavisi

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GİRİŞ

Dünyada her yıl yaklaşık 1,6 milyon yeni prostat kanseri tanısı konulmakta ve yılda 366 bin kişi bu hastalıktan ölmektedir(1). Prostat kanserine bağlı ölümler tüm kansere bağlı ölümler içinde 2. sırayı almaktadır(2). Prostat kanserine bağlı ölümler son yıllarda azalmıştır. Bunun sebebi prostat spesifik antijen (PSA) taramaları ile daha erken evrede hastalara tanı konulması ve daha etkili ilaçların bu hastalarda kullanıma girmesine bağlanmaktadır(3). Bu hastalığın androjen bağımlı olduğunun saptanmasından sonra, ilerlemiş hastalığı olan hastalarda androjen deprivasyon tedavisi (ADT) başrolü üstlendi(4) ve cerrahi kastrasyona göre daha çok tercih edilmeye başlandı. Ne yazık ki hastalar başlangıçta ADT'ye yanıt vermelerine rağmen, yaklaşık 5 yıl içinde bu grup ilaçlara direnç gelişmekte ve hastalar kastrasyona dirençli hale gelmektedir(5). Kastrasyon dirençli prostat kanseri tanımı prostat kanseri çalışma grubu (prostate cancer working group-PCWG) 3 tarafından yapıldı. Bu tanıma göre kastrasyon dirençli prostat kanseri; testesteron seviyesi 50 ng/dl'nin altında iken; PSA değeri 2 ng/dl' nin üzerinde olmak koşulu ile bir hafta ara ile ölçülen üç PSA değerinden ikisinde %50'den fazla artış olması şeklinde belirlendi(6).

Androjenlerin hem metabolik hem de anabolik etkileri bulunmaktadır. Bu etkilerini androjen reseptörlerine (AR) bağlanarak gösterirler(7). AR'nün; ligand bağlama, DNA bağlama ve bunların dışında fosforilasyon bölgeleri bulunmaktadır. Bir ligand AR'üne bağlandığı zaman reseptör stoplazmadan hücre çekirde-

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nmCRPC tedavisinde hangi ilacın seçileceği kararı, takip eden doktorun tecrübesine kalmaktadır.

KAYNAKLAR

1. Perner CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. *Cold Spring Harb Perspect Med*. 2018 Dec;8(12):a030361.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020 Jan;70(1):7–30.
3. Dickinson J, Shane A, Tonelli M, Gorber SC, Joffres M, Singh H, et al. Trends in prostate cancer incidence and mortality in Canada during the era of prostate-specific antigen screening. *CMAJ Open*. 2016 Mar 1;4(1):E73–9.
4. Huggins C, Hodges CV. Studies on Prostatic Cancer: I. The Effect of Castration, Of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. *CA Cancer J Clin*. 1972 Jul 1;22(4):232–40.
5. Lorient Y, Supiot S, Beauval JB, Schlürmann F, Pasticier G, Sargos P, et al. Management of non-metastatic castrate-resistant prostate cancer: A systematic review. *Cancer Treat Rev*. 2018 Nov;70:223–31.
6. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016 Apr 20;34(12):1402–18.
7. Roy AK, Lavrovsky Y, Song CS, Chen S, Jung MH, Velu NK, et al. Regulation of Androgen Action. In: *Vitamins & Hormones* [Internet]. Elsevier; 1998 [cited 2023 Aug 7]. p. 309–52. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0083672908609383>
8. Crawford ED, Schellhammer PF, McLeod DG, Moul JW, Higano CS, Shore N, et al. Androgen Receptor Targeted Treatments of Prostate Cancer: 35 Years of Progress with Antiandrogens. *J Urol*. 2018 Nov;200(5):956–66.
9. Culig Z, Santer FR. Androgen receptor signaling in prostate cancer. *Cancer Metastasis Rev*. 2014 Sep;33(2–3):413–27.
10. Ahmed A, Ali S, Sarkar FH. Advances in Androgen Receptor Targeted Therapy for Prostate Cancer: ANDROGEN RECEPTOR TARGETED THERAPY FOR PCa. *J Cell Physiol*. 2014 Mar;229(3):271–6.
11. Beer TM, Armstrong AJ, Rathkopf DE, Lorient Y, Sternberg CN, Higano CS, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. *N Engl J Med*. 2014 Jul 31;371(5):424–33.
12. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira De Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med*. 2019 Jul 4;381(1):13–24.
13. El-Amm J, Aragon-Ching JB. The Current Landscape of Treatment in Non-Metastatic Castration-Resistant Prostate Cancer. *Clin Med Insights Oncol*. 2019 Jan;13:117955491983392.
14. Saad F, Bögemann M, Suzuki K, Shore N. Treatment of nonmetastatic castration-resistant prostate cancer: focus on second-generation androgen receptor inhibitors. *Prostate Cancer Prostatic Dis*. 2021 Jun;24(2):323–34.
15. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. Filleur S, editor. *PLOS ONE*. 2015 Oct 13;10(10):e0139440.
16. Wade C, Kyprianou N. Profiling Prostate Cancer Therapeutic Resistance. *Int J Mol Sci*. 2018 Mar 19;19(3):904.
17. Oefelein MG, Ricchiuti VS, Conrad PW, Goldman H, Bodner D, Resnick MI, et al. Clinical

- predictors of androgen-independent prostate cancer and survival in the prostate-specific antigen era. *Urology*. 2002 Jul;60(1):120–4.
18. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*. 2008 Nov;9(11):1039–47.
19. Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, et al. Predictors of Time to Metastasis in Castration-resistant Prostate Cancer. *Urology*. 2016 Oct;96:171–6.
20. De Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res*. 2008 Oct 1;14(19):6302–9.
21. Taneja SS. Imaging in the diagnosis and management of prostate cancer. *Rev Urol*. 2004;6(3):101–13.
22. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic Efficacy of ⁶⁸ Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol*. 2016 May;195(5):1436–43.
23. Gravis G, Boher JM, Joly F, Soulié M, Albiges L, Priou F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. *Eur Urol*. 2016 Aug;70(2):256–62.
24. Xie W, Regan MM, Buyse M, Halabi S, Kantoff PW, Sartor O, et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol*. 2017 Sep 20;35(27):3097–104.
25. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. *Science*. 2009 May 8;324(5928):787–90.
26. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol*. 2016 Jun 20;34(18):2098–106.
27. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2018 Jun 28;378(26):2465–74.
28. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020 Jun 4;382(23):2197–206.
29. Clegg NJ, Wongvipat J, Joseph JD, Tran C, Ouk S, Dilhas A, et al. ARN-509: A Novel Antiandrogen for Prostate Cancer Treatment. *Cancer Res*. 2012 Mar 15;72(6):1494–503.
30. Fujita K, Nonomura N. Role of Androgen Receptor in Prostate Cancer: A Review. *World J Mens Health*. 2019;37(3):288.
31. Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, et al. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. *Eur Urol*. 2016 Dec;70(6):963–70.
32. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. 2018 Apr 12;378(15):1408–18.
33. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and Overall Survival in Prostate Cancer. *Eur Urol*. 2021 Jan;79(1):150–8.
34. Small EJ, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Final survival results

- from SPARTAN, a phase III study of apalutamide (APA) versus placebo (PBO) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC). *J Clin Oncol*. 2020 May 20;38(15_suppl):5516–5516.
35. Leibowitz–Amit R, Joshua AM. Targeting the Androgen Receptor in the Management of Castration-Resistant Prostate Cancer: Rationale, Progress, and Future Directions. *Curr Oncol*. 2012 Dec 1;19(11):22–31.
 36. Moilanen AM, Riikonen R, Oksala R, Ravanti L, Aho E, Wohlfahrt G, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. *Sci Rep*. 2015 Jul 3;5(1):12007.
 37. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2019 Mar 28;380(13):1235–46.
 38. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. *N Engl J Med*. 2020 Sep 10;383(11):1040–9.
 39. Thakur A, Roy A, Ghosh A, Chhabra M, Banerjee S. Abiraterone acetate in the treatment of prostate cancer. *Biomed Pharmacother*. 2018 May;101:211–8.
 40. Ryan CJ, Crawford ED, Shore ND, Underwood W, Taplin ME, Londhe A, et al. The IMAA-GEN Study: Effect of Abiraterone Acetate and Prednisone on Prostate Specific Antigen and Radiographic Disease Progression in Patients with Nonmetastatic Castration Resistant Prostate Cancer. *J Urol*. 2018 Aug;200(2):344–52.
 41. Zurth C, Sandman S, Trummel D, Seidel D, Nubbemeyer R, Gieschen H. Higher blood–brain barrier penetration of [¹⁴ C]apalutamide and [¹⁴ C]enzalutamide compared to [¹⁴ C]darolutamide in rats using whole-body autoradiography. *J Clin Oncol*. 2019 Mar 1;37(7_suppl):156–156.