

# 13. BÖLÜM

## TİROİD KANSERİNDE İMMÜNÖTERAPİNİN YERİ

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### GİRİŞ

Tiroid kanseri (TK), her yıl teşhis edilen tüm kanserlerin %4'ünü oluşturur ve en sık görülen endokrin malignitedir (1). Yapılan popülasyona dayalı bir çalışmada hastaların %76'sının kadın olduğu, tiroid kanserinin kadınları erkeklerden üç kat daha fazla etkilediği bildirilmiştir (2).

Tiroid foliküler hücrelerinin dönüşümü, foliküler hücre karsinogenezinin en çok kabul gören teorisi olan çok aşamalı bir süreç yoluyla diferansiye veya az diferansiye TK'ye neden olabilir. Tiroid kanserleri, foliküler hücrelerden köken alan, papiller, foliküler, hurthle hücresi ve anaplastik karsinomlar ile parafoliküler veya C hücrelerinden köken alan medüller tiroid kanseri gibi farklı histolojik tipler olarak kategorize edilirler (3).

TK'nin %90'ından fazlasını oluşturan Diferansiye TK, Papiller TK (PTK), Foliküler TK (FTK) ve Hurtle Hücreli Karsinomlar (HHK) iyi farklılaşmış olup, tiroid hücre organizasyonunun sürdürülmesi ile karakterize edilir. Bu farklılaşmış kanserleri olan hastalar, %95'in üzerinde 5 yıllık sağkalım oranı ile iyi bir prognoza sahiptir (2,4).

Anaplastik tiroid karsinomu (ATK), tüm tiroid kanserlerinin yalnızca %1-2'sini oluşturan nadir bir tiroid kanseri türüdür ve TK'ye bağlı ölümlerin yarısından fazlasını oluşturmaktadır (5). Hastaların çoğu 50 yaşın üzerindedir ve hastalığın ilerlemesi çok hızlı olup tümör boyutu 1 hafta içinde ikiye katlanır (6).

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seçenek olabileceğini düşündürmektedir. Ancak yanıt oranını daha iyi değerlendirmek ve uzun vadeli etkinliği belirlemek için daha ileri prospektif çalışmalara ihtiyaç vardır.

## KAYNAKLAR

1. Seib CD, Sosa JA. Evolving understanding of the epidemiology of thyroid cancer. *Endocrinol Metab Clin N Am*. 2019;48:23–35.
2. Maso LD, Tavilla A, Pacini F, et al. Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. *Eur. J. Cancer* 2017;77:140–152.
3. Nowell PC. The clonal evolution of tumor cell populations. *Science*. 1976; 194:23–8. doi: 10.1126/science.959840
4. Cancer of the Thyroid—Cancer Stat Facts [Internet]. SEER. Available online: <https://seer.cancer.gov/statfacts/html/thyro.html> (accessed on 2 August 2019).
5. Ne RL, Farrar WB, Kloos RT, et al. Anaplastic Thyroid Cancer. *Endocrinol. Metab. Clin. N. Am.* 2008;37:525–538.
6. Ain, K. Anaplastic Thyroid Carcinoma: Behavior, Biology, and Therapeutic Approaches. *Thyroid. O. J. Am. Thyroid. Assoc.* 1998; 8: 715–726.
7. Prasongsook N, Kumar A, Chintakuntlawar AV, et al. Survival in response to multimodal therapy in anaplastic thyroid cancer. *J. Clin. Endocrinol. Metab.* 2017; 102:4506–4514.
8. Neff RL, Farrar WB, Kloos RT, et al. Anaplastic thyroid cancer. *Endocrinol Metab Clin North Am* 2008;37(2):525–38. xi.
9. Cabanillas ME, Zafero M, Gunn GB, et al. Anaplastic thyroid carcinoma: treatment in the age of molecular targeted therapy. *J. Oncol. Pract.* 12, 511–8 (2016)
10. Pacini F, Castagna MG, Cipri C, et al. Medullary thyroid carcinoma. *Clin. Oncol. R. Coll. Radiol G B.* 2010; 22:475–485.
11. Leboulleux S, Baudin E, Travagli J, et al. Medullary thyroid carcinoma. *Clin. Endocrinol. (Oxf)*. 2004; 61: 299–310.
12. Besic N, Hocevar M, Zgajnar J, et al. Prognostic factors in anaplastic carcinoma of the thyroid—A multivariate survival analysis of 188 patients. *Langenbeck's Arch. Surg.* 2004; 390: 203–208.
13. Mazzaferri EL. An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid.* (1999) 9:421–7.
14. Haugen BR. American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? *Cancer* 2017 123, 372–381 (2015).
15. Nguyen QT, Lee EJ, Huang MG, et al. Diagnosis and treatment of patients with thyroid cancer. *Am Health Drug Benefits.* 2015;8(1):30–40.
16. National Comprehensive Cancer Network I: NCCN clinical practice guidelines in oncology - thyroid carcinoma v1.2016. In. Edited by 1.2016; 2016.

17. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med.* 2015;372:621-630.
18. Salama AK, Flaherty KT. BRAF in melanoma: current strategies and future directions. *Clin Cancer Res.* 2013;19:4326-4334.
19. He J, Hu Y, Hu M, et al. Development of PD-1/PD-L1 pathway in tumor immune microenvironment and treatment for non-small cell lung cancer. *Sci Rep.* 2015;5:13110.
20. Cao Y, Zhang L, Kamimura Y, et al. B7-H1 overexpression regulates epithelial-mesenchymal transition and accelerates carcinogenesis in skin. *Cancer Res.* 2011;71:1235-1243.
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* (2011) 144:646-74.
22. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med.* (1986) 315:1650-9.
23. Peggs KS, Quezada SA, Chambers CA, et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. *J. Exp. Med.* 2009; 206: 1717-1725.
24. Ahn S, Kim TH, Kim SW, et al. Comprehensive screening for PD-L1 expression in thyroid cancer. *Endocr Relat Cancer.* 2017;24:97-106.
25. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med.* 2002;8:793-800.
26. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol.* 2008;8:467-477.
27. Bastman JJ, Serracino HS, Zhu Y, et al. Tumor-infiltrating T cells and the PD-1 checkpoint pathway in advanced differentiated and anaplastic thyroid cancer. *J Clin Endocrinol Metab.* 2016;101:2863-2873.
28. Zamani MR, Aslani S, Salmaninejad A, et al. PD-1/PD-L and autoimmunity: A growing relationship. *Cell. Immunol.* 2016; 310: 27-41.
29. Spranger S, Gajewski TF. Impact of oncogenic pathways on evasion of antitumour immune responses. *Nat Rev Cancer.* 2018;18:139-147.
30. Kondo A, Yamashita T, Tamura H, et al. Interferon-gamma and tumor necrosis factor-alpha induce an immunoinhibitory molecule, B7-H1, via nuclear factor-kappaB activation in blasts in myelodysplastic syndromes. *Blood.* 2010;116:1124-1131.
31. Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med.* 2012;4:127ra37
32. Corthay A. How do regulatory T cells work? *Scand J Immunol.* 2009;70:326-336.
33. Haxhinasto S, Mathis D, Benoist C. The AKT-mTOR axis regulates de novo differentiation of CD4+Foxp3+ cells. *J Exp Med.* 2008;205:565-574.
34. Huang Y, Ma C, Zhang Q, et al. CD4+ and CD8+ T cells have opposing roles in breast cancer progression and outcome. *Oncotarget.* 2015;6:17462-17478.
35. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev.* 2010;236:219-242.
36. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. *Trends Mol Med.* 2015;21:24-33.

37. Angell TE, Lechner MG, Jang JK, Correa AJ, LoPresti JS, Epstein AL. BRAF V600E in papillary thyroid carcinoma is associated with increased programmed death ligand 1 expression and suppressive immune cell infiltration. *Thyroid*. 2014;24:1385-1393
38. Wei SC, Levine JH, Cogdill AP, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell*. 2017;170:1120-1133.e17.
39. Sanborn RE, Pishvain MJ, Callahan MK, et al. Phase I results from the combination of an immune-activating anti-CD27 antibody (varlilumab) in combination with PD-1 blockade (nivolumab): activation across multiple immune pathways without untoward immune-related adverse events. *Cancer Res*. 2016;76(14 suppl):abstract.
40. Liotti, F.; Prevete, N.; Vecchio, G.; Melillo, R.M. Recent advances in understanding immune phenotypes of thyroid carcinomas: Prognostication and emerging therapies. *F1000Res* 2019, 28, 8.
41. Landa I, Ibrahimasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J. Clin. Investig*. 2016; 126:1052–1066.
42. Bongiovanni M, Rebecchini C, Saglietti C, et al. Very low expression of PD-L1 in medullary thyroid carcinoma. *Endocr. Relat. Cancer* 2017; 24: L35–L38.
43. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer*. 2013;13:184-199.
44. Na KJ, Choi H. Immune landscape of papillary thyroid cancer and immunotherapeutic implications. *Endocr. Relat. Cancer* 2018; 25:523–531.
45. Shi RL, Qu N, Luo TX, et al. Programmed death-ligand 1 expression in papillary thyroid cancer and its correlation with clinicopathologic factors and recurrence. *Thyroid*. 2017;27:537-545.
46. Riella, LV, Paterson AM, Sharpe AH, et al. Role of PD-1 pathway in the immune response. *Am. J. Transplant*. 2012; 12:2575–2587.
47. Lorusso L, Cappagli V, Valerio L, et al. Thyroid Cancers: From Surgery to Current and Future Systemic Therapies through Their Molecular Identities. *Int. J. Mol. Sci*. 2021;;22: 3117. <https://doi.org/10.3390/ijms22063117>.
48. Min IM, Shevlin E, Vedvyas Y, et al. CAR T Therapy Targeting ICAM-1 Eliminates Advanced Human Thyroid Tumors. *Clin Cancer Res*. 2017; 23(24): 7569–83.
49. French JD, Haugen BR: Thyroid-Specific T Cells in Patients With Differentiated Thyroid Cancer: Implications for Immune-Based Therapies? *J Clin Endocrinol Metab*. 2017; 102(7): 2131–2.
50. Ehlers M, Kuebart A, Hautzel H, et al. Epitope-Specific Antitumor Immunity Suppresses Tumor Spread in Papillary Thyroid Cancer. *J Clin Endocrinol Metab*. 2017; 102(7): 2154–61.
51. Naoum GE, Morkos M, Kim B, et al. Novel targeted therapies and immunotherapy for advanced thyroid cancers. *Mol Cancer*. 2018; 17(1): 51.
52. Mehnert, J.M.; Varga, A.; Brose, M.S.; Aggarwal, R.R.; Lin, C.C.; Prawira, A.; De Braud, F.; Tamura, K.; Doi, T.; Piha-Paul, S.A.; et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. *BMC Cancer* 2019, 19.

53. Mehnert JM, Varga A, Brose M, et al. Pembrolizumab for advanced papillary or follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 study. *J Clin Oncol* 2016;34(15\_suppl):6091.
54. Iyer PC, Dadu, R, Gule-Monroe M, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. *J. Immunother. Cancer* 2018; 6: 68.
55. Capdevila J, Wirth, LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. *J. Clin. Oncol.* 2020, 38, 2620–2627.
56. C. Dierks, J. Seufert, J Ruf, et al. 1915P The lenvatinib/pembrolizumab combination induces long lasting and complete responses in patients with metastatic anaplastic or poorly differentiated thyroid carcinoma: Results from a retrospective study and first results from the prospective phase II ATLEP trial. *Annals of Oncology*. Volume 31, Supplement 4, September 2020, Page S1085. <https://doi.org/10.1016/j.annonc.2020.08.1403>.
57. Kollipara R, Schneider B, Radovich M, et al. Exceptional Response with Immunotherapy in a Patient with Anaplastic Thyroid Cancer. *Oncologist*2017;22:1149–1151.
58. Sherman EJ, Tsai CJ, Zhi WI, et al. Pilot study combining PD-L1 antibody durvalumab (D) with CTLA-4 antibody tremelimumab (T) and stereotactic body radiotherapy (SBRT) to treat metastatic anaplastic thyroid cancer (ATC). *J. Clin. Oncol.* 2019; 37: 6088.
59. Voron, T. et al. Control of the immune response by pro-angiogenic factors. *Front. Oncol.* 4, 70 (2014).
60. Fukumura D, Kloepper J, Amoozgar Z, et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat. Rev. Clin. Oncol.* 15, 325–340 (2018).