

Bölüm 43

PULMONER TOKSİTE VE YÖNETİMİ

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GİRİŞ

Günümüzde kanser immünoterapisi denilince akla ilk olarak immün kontrol noktası inhibitörleri (KNİ) gelmektedir. Tümöre karşı immün sistemi güçlendirmek için kullanılan immünmodülatör antikolar olan ve ileri evre malignitesi olan hastalarda prognozu önemli ölçüde iyileştiren KNİ'ler kanser tedavisinde dönüm noktası olmuştur (1). Tek başlarına veya diğer kemoterapi ajanları ile kombine edildiklerinde immün ilişkili advers olaylara (İİAO) neden olmaktadır (2). KNİ'leri, Programlanmış hücre ölüm-1 (PD-1), PD-1 ligandı (PD-L1) reseptörleri ve Sitotoksik T-lenfosit-iliskili antijen 4 (CTLA-4) gibi immün kontrol noktası proteinlerinin negatif yöndeki düzenleyici etkisini bloke ederek tümöre spesifik immüniteyi güçlendirirken farklı organlarındaki aktif T lenfositleri üzerindeki freni kaldırır. Bu T hücrelerinin tetiklediği otoantikolar, inflamatuvar sitokinler ve kompleman aracılı inflamasyonun normal doku hücrelerinde oluşturduğu hasarın, İİAO'ların temel oluş mekanizması olduğu düşünülmektedir (3). KNİ ile ilişkili pnömonitis (KNİ-P), KNİ'lerinin göreceli olarak nadir fakat ağır ve ölümcül seyretme potansiyeli olan bir komplikasyondur. Deri toksitesi, hepatit, tiroitit ve kolitten sonra en sık görülen İİAO'dır (4-6).

Bu yazıda ağırlıklı olarak KNİ-P'in epidemiyolojisi, klinik ve radyolojik özellikleri, tanı ve tedavisi üzerinde durulacaktır. Diğer KNİ ile ilişkili pulmoner komplikasyonlar "ayırıcı tanı" başlığı altında ele alınacaktır.

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KAYNAKÇA

1. Li, Y, Li, F, Jiang, F, et al. A mini-review for cancer immunotherapy: Molecular understanding of PD-1/PD-L1 pathway and translational blockade of immune checkpoints. *Int. J. Mol. Sci.* 2009;17(7):1-22.
2. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015; 26: 2375-91.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 378: 158-68.
4. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. *JAMA Oncol* 2016; 2:1607-16.
5. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with Anti-Programmed Death-1/Programmed Death Ligand 1 therapy. *J Clin Oncol* 2017; 35:709-17.
6. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest* 2017; 152:271-81.
7. Cadranell J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. *Eur Respir Rev* 2019; 28: 190058. doi: org/10.1183/16000617.0058-2019.
8. Ma K, Lu Y, Jiang S, et al. The relative risk and incidence of immune checkpoint inhibitors related pneumonitis in patients with advanced cancer: a meta-analysis. *Front Pharmacol* 2018; 9: 1430. doi: 10.3389/fphar.2018.01430.
9. Xu C, Chen YP, Du XJ, et. Al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. *BMJ.* 2018 Nov 8;363: k4226. doi: 10.1136/bmj.k4226.
10. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* 2012; 13(5):459-65
11. Su Q, Zhu EC, Wu J-B, et al. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. *Front Immunol* 2019; 10: 108. doi: 10.3389/fimmu.2019.00108.
12. Shibaki R, Murakami S, Matsumoto Y, et al. Association of immune-related pneumonitis with the presence of preexisting interstitial lung disease in patients with non-small lung cancer receiving anti-programmed celldeath 1 antibody. *Cancer Immunol Immunother.* 2020;69(1):15-22.
13. Yamaguchi T, Shimizu J, Hasegawa T et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: A retrospective analysis. *Lung Cancer* 2018; 125: 212-7.
14. Antonia SJ, Villegas A, Daniel D, et al. PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;13;379(24):2342-50. doi:10.1056/NEJMoa1809697.
15. Voong KR, Hazell SZ, Fu W, et al. Relationship between prior radiotherapy and checkpoint-inhibitor pneumonitis in patients with advanced non-small-cell lung cancer. *Clin Lung Cancer* 2019;20(4): e470-e9. doi: 10.1016/j.clcc.2019.02.018
16. Suresh K, Voong KR, Shankar B, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. *J Thorac Oncol* 2018; 13: 1930-9.
17. O’Kane GM, Labbé C, Doherty MK, et al. Monitoring and management of immune-related adverse events associated with programmed cell death protein-1 axis inhibitors in lung cancer. *Oncologist* 2017; 22:70-80.
18. Franzen D, Schad K, Kowalski B, et al. Ipilimumab and early signs of pulmonary toxicity in patients with metastatic melanoma: a prospective observational study. *Cancer Immunol Immunother* 2018; 67: 127-34.

19. Barjaktarevic IZ, Qadir N, Suri A, et al. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. *Chest* 2013; 143: 858-61.
20. Powell CA. Pulmonary infiltrates in a patient with advanced melanoma. *J Clin Oncol* 2017; 35: 705-8.
21. Sano T, Uhara H, Mikoshiba Y, et al. Nivolumab-induced organizing pneumonia in a melanoma patient. *Jpn J Clin Oncol* 2016; 46: 270-2.
22. V.L. Chiou, M. Burotto, Pseudoprogression and immune-related response in solid tumors, *J. Clin. Oncol.* 2015; 33 (31):3541-3.
23. Wang Q, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. *Int Immunopharmacol.* 2018; 58:125-35.
24. Wang H, Guo X, Zhou J, et al. Clinical diagnosis and treatment of immune checkpoint inhibitor-associated pneumonitis. *Thorac Cancer.* 2020 ;11(1):191-7
25. Del Castillo M, Romero FA, et al. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis* 2016; 63: 1490-3.
26. Anastasopoulou A, Ziogas DC, Samarkos et al. Reactivation of tuberculosis in cancer patients following administration of immune checkpoint inhibitors: current evidence and clinical practice recommendations. *J Immunother Cancer.* 2019;7(1):239. doi: 10.1186/s40425-019-0717-7.
27. Thore P, Godbert B, Petit I, Chaouat A. Radiation recall pneumonitis in a patient treated by nivolumab for non-small-cell lung cancer, no relapse with rechallenge. *J. Med. Oncol.* 2018; 1(3):12.
28. McGovern K, Ghaly M, Esposito M, et al. Radiation recall pneumonitis in the setting of immunotherapy and radiation: a focused review. *Future Sci OA.* 2019;5(5): FSO378. doi:10.2144/fsoa-2018-0123.
29. Rambhia PH, Reichert B, Scott JF, et al. Immune checkpoint inhibitor-induced sarcoidosis-like granulomas. *Int J Clin Oncol.* 2019;24(10):1171-81.
30. Haanen JBAG, Carbone F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: Suppl. 4, iv119–iv142.
31. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; 36: 1714-68.
32. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; 5: 95.
33. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
34. Sears CR, Peikert T, Possick JD, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An official American Thoracic Society research statement. *Am J Respir Crit Care Med.* 2019;200(6):e31-e43. doi: 10.1164/rccm.201906-1202ST