

MALİGN MELANOM'DA GERİATRİK HASTA YÖNETİMİ

41. BÖLÜM

Gökçen Tuğba ÇEVİK¹

GİRİŞ

Melanom, melanositlerin malign tümörü olup morbiditesi ve mortalitesi yüksek bir hastalıktır. İnsidansı tüm dünyada hızla artmaktadır. İnsidansın en yüksek olduğu yerler gelişmiş ülkelerdir. Sağlık Bakanlığı verilerine göre ülkemizde 2014 yılında yeni olgu hızı 100.000 kişide erkeklerde 1.8, kadınlarda ise 1.2 dir. Hastalığın etyolojisinde suçlanan temel faktör, yürütücü mutasyonların oluşmasını sağlayarak karsinogenez yollarının ilerlemesine neden olan UV ışınlarıdır.

Melanom tedavisinin temelini erken tanı ve cerrahi eksizyon oluşturmaktadır. Erken evrede uygun cerrahi ile uzun süreli sağ kalım beklenmekle birlikte ileri evre hastalıkta sonuçlar yüz güldürücü değildir. İçinde bulunduğumuz on yılda malign melanomda kullanıma giren immun kontrol noktası inhibitörleri ile MAPK yolağında görevli enzimleri hedefleyen BRAF ve MEK inhibitörleri son dönemde metastatik hastalıkta sağkalım avantajı göstermiştir.

YAŞLI MALİGN MELANOM HASTASINDA EPİDEMİYOLOJİ VE ONKOGERİYATRİK DEĞERLENDİRME

Malign melanom vakalarının % 40'ından fazlası farklı klinikopatolojik özellikler ile birlikte ≥ 65 yaş üzerinde teşhis edilir (1). Yaşlı hastalar sıklıkla daha büyük breslow kalınlığı, artmış ülserasyon sıklığı, artmış mitotik index gibi iyi tanımlanmış negatif prognostik faktörler ile birlikte hastalığın ileri evrelerinde teşhis edilir (2). Hatta yukarıda belirtilen özelliklerle ilişkisi dikkate alınarak ileri yaş, melanomda bağımsız bir kötü prognostik faktör olarak ele alınır (3). Son otuz yılda malign melanomlu genç erişkinlerde görülen mortalitede iyileşmenin aksine yaşlılarda mortalite sabit kaldı. Farklı biyolojik ve moleküler profiller, im-

¹ Uzm. Dr, Uşak Üniversitesi Eğitim Araştırma Hastanesi, gokcen-8@hotmail.com

KAYNAKLAR

1. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. *Advances in Experimental Medicine and Biology*, 810, 120–140.
2. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. *Journal of Clinical Oncology*, 19(16), 3622–3634.
3. Balch CM, Soong SJ, Gershenwald JE, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. *Annals of Surgical Oncology*, 20(12), 3961–3968.
4. Balch CM, Thompson JF, Gershenwald, JE, et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: An inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. *Annals of Surgical Oncology*, 21(4), 1075–1081.
5. Conway WC, Faries MB, Nicholl MB, et al. Age-related lymphatic dysfunction in melanoma patients. *Annals of Surgical Oncology*, 16(6), 1548–1552.
6. Extermann M & Hurria A. Comprehensive geriatric assessment for older patients with cancer. *Journal of Clinical Oncology*, 25(14), 1824–1831.
7. Coit DG, Thompson JA, Algazi A, et al. Melanoma, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016;14(4):450–73.
8. Goronzy JJ, Fang F, Cavanagh MM, et al. Naive T cell maintenance and function in human aging. *The Journal of Immunology*, 194(9), 4073–4080.
9. Basile D, Garattini SK, Bonotto M, et al. Immunotherapy for colorectal cancer: Where are we heading? *Expert Opinion on Biological Therapy*, 17 (6), 709-721.
10. Mocellin S, Pasquali S, Rossi CR, et al. Interferon alpha adjuvant therapy in patients with high-risk melanoma: A systematic review and meta-analysis. *Journal of the National Cancer Institute*, 102(7), 493–501.
11. Ciocan D, Barbe C, Aubin F, et al. Distinctive features of melanoma and its management in elderly patients: A population-based study in France. *JAMA Dermatology*, 149(10), 1150–1157.
12. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: Long term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. *European Journal of Cancer (Oxford, England: 1990)*, 119, 1–10.
13. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. *Journal of Clinical Oncology*, 35(7), 785–792.
14. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *The New England Journal of Medicine*, 378(19), 1789–1801.
15. Okazaki T, Iwai Y, Honjo T. New regulatory co-receptors: Inducible co-stimulatory and PD-1. *Current Opinion in Immunology*, 14(6), 779–782.
16. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *The New England Journal of Medicine*, 363(8), 711–723.
17. Maio M., Grob JJ, Aamdal S, Bondarenko I, et al. Five-year survival rates for treatment-naïve patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *Journal of Clinical Oncology*, 33(10), 1191–1196.
18. Chiarion Sileni V, Pigozzo J, Ascierto PA, et al. Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded Access programme. *Journal of Experimental & Clinical Cancer Research: CR*, 33, 30.
19. Singh H, Kim G, Maher VE, et al. FDA subset analysis of the safety of nivolumab in elderly patients with advanced cancers. *Journal of Clinical Oncology*, 34(15_suppl), 10010.
20. Weber JS, D'Angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology*, 16(4), 375–384.

21. Ascierto PA, Long, GV, Robert C, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncology*, 5(2), 187–194.
22. Robert C, Ribas A, Wolchok JD, et al. Anti programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. *Lancet (London,England)*, 384(9948), 1109–1117.
23. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *The Lancet Oncology*, 20(9), 1239–1251.
24. Larkin, J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *The New England Journal of Medicine*, 381(16), 1535–1546.
25. Orloff M. Melanoma immunotherapy in the elderly. *Current Oncology Reports*, 20, 20.
26. Ridolfi L, De Rosa F, Petracci E, et al. Anti-PD1 antibodies in patients aged ≥ 75 years with metastatic melanoma: A retrospective multicentre study. *Journal of GeriatricOncology*, 11(3), 515–522.
27. Bastholt L, Schmidt H, Bjerregaard JK, et al. Age favoured overall survival in a large population-based Danish patient cohort treated with anti-PD1 immune check point inhibitor for metastatic melanoma. *EuropeanJournal of Cancer*, 119, 122–131.
28. Larkin j, Chiarion-Sileni v, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *The New England Journal of Medicine*. 373(1), 23–34.
29. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose -ranging study. *The Lancet. Oncology*, 11(2), 155–164.
30. Ascierto PA, Simeone E, Sileni VC, et al. Clinical experience with ipilimumab 3mg/kg: Real-world efficacy and safety data from an expanded access programme cohort. *Journal of Translational Medicine*, 12, 116.
31. Singh H, Kim G, Maher VE, et al. FDA subset analysis of the safety of nivolumab in elderly patients with advanced cancers. *Journal of Clinical Oncology*, 34(15_suppl), 10010.
32. Friedman CF, Horvat TZ, Minehart J, et al. Efficacy and safety of check point blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). *Journal of ClinicalOncology*, 34(15_suppl), 10009.
33. Larkin J, Chiarion-Sileni V, Gonzalez, R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *The New England Journal of Medicine*, 381(16), 1535–1546.
34. Kapoor V, Rixe O. Toxicity of PD-1/CTLA-4inhibitor immunotherapy among elderly patients. *Journal of Clinical Oncology*, 37(15_suppl), e14139.
35. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011 Jun 30;364(26):2507–16.
36. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014 Nov 13;371(20):1877–88.
37. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015 Aug 1; 386(9992):444–51.
38. Robert C, Karaszewska B, Schacter J. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib+ trametinib in patients with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma (abstract LBA40). *European Society for Medical Oncology meeting; 2016 [RefType: Abstract]*.
39. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014Nov 13;371(20):1867–76

40. Sullivan RY, Weber JS, Patel SP. A phaseIb/II study of BRAF inhibitor (BRAFi) encorafenib (ENCO) plus MEK inhibitor (MEKi) binimetinib (BINI) in cutaneous melanoma patients naive to BRAFi treatment. *J Clin Oncol* 2015;33(suppl abstract9007) [RefType: Abstract]
41. Lacouture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist* 2013;18(3):314–22.
42. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Acad Dermatol* 2019;80(1):208–50.
43. Trotter SC, Sroa N, Winkelmann RR, et al. A global review of melanoma follow-up guidelines. *J Clin Aesthet Dermatol* 2013;6(9):18–26.