

Bölüm 15

MEME KANSERİNDE İMMÜNÖTERAPİ

Melih ŞİMŞEK¹

GİRİŞ

İmmüno-onkolojide son yıllarda çok hızlı gelişmeler yaşanmaktadır. Bu yenilikler doğrultusunda pek çok farklı kanser tipinde özellikle immün kontrol noktası inhibitörleri (İKİ) ile olumlu sonuçlar bildirilmektedir. Monoklonal antikor yapısındaki bu ajanlar, sitotoksik T lenfosit antijeni-4 (CTLA-4), programlı hücre ölümü proteini-1 (PD-1) ve PD-1 ligandını (PD-L1) hedef almaktadır. Kemoterapiden (KT) farklı olarak immünoterapi (İT) ajanlarının etkisi geç ortaya çıkmakta ancak belirgin ve uzun süreli klinik yanıtlar elde edilmektedir. Farklı tümör tiplerinde etkinlikleri gösterilen bu ajanlarla ilgili her geçen gün yeni çalışma sonuçları açıklanmaktadır. Diğer birçok kanser tipi ile karşılaştırıldığında, meme kanserinde İT ajanları ile ilgili klinik çalışmalar ise hala gelişme aşamasındadır. Ancak özellikle immün kontrol noktası blokajı, erken faz çalışmalarında klinik aktivite göstermiş olup makul güvenlik profiline sahip görünmektedir.

Meme kanseri, tüm dünyada kadınlarda en çok görülen kanser tipi olup kansere bağlı ölümlerde de ikinci sırada yer almaktadır (Bray et al. 2018) (Ferlay et al. 2018) (Siegel, Miller, and Jemal 2019) (DeSantis et al. 2019). Meme kanseri zayıf immünojenik olarak bilinmekte (Alexandrov et al. 2013) ve nispeten daha düşük tümör mutasyon yükü (TMY) ile karakterize görünmektedir (Vogelstein et al. 2013). Bu nedenle de soğuk tümörler grubunda yer almaktadır (Swoboda and Nanda 2018). Diğer taraftan, PD-L1 hem tümör hücreleri hem de immün hücreler tarafından eksprese edilebilmekte ve bu ekspresyonun meme kanserinde hormon reseptör negatifliği, daha yüksek histolojik grad ve daha yüksek düzeyde TIL sayısı ile korele olduğu gözlenmektedir (Buisseret et al. 2017).

¹ Uzm. Dr., Yozgat Şehir Hastanesi, Tıbbi Onkoloji, mdmelih@gmail.com

HER2-pozitif meme kanseri diğer meme kanseri alt tiplerine göre daha immünojeniktir ve bu alt tiplerde İT çalışmaları yoğunlaşmaktadır. Özellikle TNMK'de tedavi edilebilir hedefler olmadığından, bu hastalıkta elde edilecek iyi sağkalım sonuçları büyük önem kazanmaktadır.

Ne yazık ki hala immüno-onkoloji ajanlarının hangi hasta grubunda daha etkili olduğu bilinmemekte ve prediktif belirteçler araştırılmaktadır. Standart tedavi ve hedefe yönelik tedavilerin İKİ ile kombinasyonunun immün düzenlemede iyileşme sağlayarak daha iyi sağkalıma yol açacağı düşünülmektedir. Ancak yine hangi kombinasyonun daha iyi sonuç vereceği bilinmemektedir. Seçilmiş hastaya, en etkili tedavinin, en az yan etki ile uygulanmasının ideal olduğu artık kabul görmektedir. Her ne kadar immüno-onkolojide önemli ilerlemeler olsa da, meme kanserinde ideal tedavinin ortaya konması için hala zamana ihtiyaç var gibi görünmektedir.

KAYNAKÇA

1. Adams S et al. (2019) 'Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study', *Ann Oncol*, 30: 405-11.
2. Adams S et al. (2019) 'Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study', *Ann Oncol*, 30: 397-404.
3. Adams S et al. (2016) 'Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC)', *Journal of Clinical Oncology*, 34: 1009-09.
4. Alexandrov LB et al. (2013) 'Signatures of mutational processes in human cancer', *Nature*, 500: 415-21.
5. Ayoub NM, Al-Shami KM & Yaghan RJ. (2019) 'Immunotherapy for HER2-positive breast cancer: recent advances and combination therapeutic approaches', *Breast Cancer (Dove Med Press)*, 11: 53-69.
6. Bianchini G & L Gianni. (2014) 'The immune system and response to HER2-targeted treatment in breast cancer', *Lancet Oncol*, 15: e58-68.
7. Bray F et al. (2018) 'Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *CA Cancer J Clin*, 68: 394-424.
8. Budczies J et al. (2015) 'Classical pathology and mutational load of breast cancer - integration of two worlds', *J Pathol Clin Res*, 1: 225-38.
9. Buisseret L et al. (2017) 'Tumor-infiltrating lymphocyte composition, organization and PD-1/PD-L1 expression are linked in breast cancer', *Oncoimmunology*, 6: e1257452.
10. Cortés J et al. (2019) 'LBA21KEYNOTE-119: Phase III study of pembrolizumab (pembro) versus single-agent chemotherapy (chemo) for metastatic triple negative breast cancer (mTNBC)', *Annals of Oncology*, 30.
11. Cortés J et al. (2018) 'KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (PBO) + chemo for previously untreated, locally recurrent, inoperable or metastatic triple-negative breast cancer (mTNBC)', *Journal of Clinical Oncology*, 36: TPS18-TPS18.
12. DeSantis CE et al. (2019) 'Breast cancer statistics, 2019', *CA Cancer J Clin*.
13. Dirix LY et al. (2018) 'Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study', *Breast Cancer Res Treat*, 167: 671-86.

14. Domchek S et al. (2016) 'MEDIOLA: A phase I/II, open-label trial of olaparib in combination with durvalumab (MEDI4736) in patients (pts) with advanced solid tumours', *Annals of Oncology*, 27.
15. Domchek SM et al. (2018) 'Abstract PD6-11: An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline *BRCA*-mutated (*BRCA*) *HER2*-negative metastatic breast cancer (MBC)', *Cancer Res*, 78: PD6-11-PD6-11.
16. Emens LA et al. (2019) 'Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study', *JAMA Oncol*, 5: 74-82.
17. Emens LA et al. (2019) 'Abstract PD3-01: Results from KATE2, a randomized phase 2 study of atezolizumab (atezo)+trastuzumab emtansine (T-DM1) vs placebo (pbo)+T-DM1 in previously treated *HER2*+ advanced breast cancer (BC)', *Cancer Res*, 79: PD3-01-PD3-01.
18. Ferlay J et al. (2018) 'Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018', *Eur J Cancer*, 103: 356-87.
19. Han Hyo S et al. (2019) 'SGNLVA-002: Single-arm, open label phase Ib/II study of ladiratuzumab vedotin (LV) in combination with pembrolizumab for first-line treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer', *Journal of Clinical Oncology*, 37: TPS1110-TPS10.
20. Hyslop T et al. (2013) 'Population and target considerations for triple-negative breast cancer clinical trials', *Biomark Med*, 7: 11-21.
21. Kim A et al. (2017) 'Programmed death-ligand 1 (PD-L1) expression in tumour cell and tumour infiltrating lymphocytes of *HER2*-positive breast cancer and its prognostic value', *Sci Rep*, 7: 11671.
22. Konstantinopoulos P et al. (2016) 'Phase I/II study of niraparib plus pembrolizumab in patients with triple-negative breast cancer or recurrent ovarian cancer (KEYNOTE-162)', *Journal of Clinical Oncology*, 34: TPS5599-TPS99.
23. Krasniqi E et al. (2019) 'Immunotherapy in *HER2*-positive breast cancer: state of the art and future perspectives', *J Hematol Oncol*, 12: 111.
24. Loi S et al. (2019) 'Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers', *J Clin Oncol*, 37: 559-69.
25. Loi S et al. (2019) 'Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, *HER2*-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial', *Lancet Oncol*, 20: 371-82.
26. Loi S et al. (2013) 'Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98', *J Clin Oncol*, 31: 860-7.
27. Loibl S et al. (2019) 'A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study', *Ann Oncol*, 30: 1279-88.
28. Malorni L et al. (2012) 'Clinical and biologic features of triple-negative breast cancers in a large cohort of patients with long-term follow-up', *Breast Cancer Res Treat*, 136: 795-804.
29. Marotti JD et al. (2017) 'Triple-Negative Breast Cancer: Next-Generation Sequencing for Target Identification', *Am J Pathol*, 187: 2133-38.
30. McArthur HL et al. (2018) 'A single-arm, phase II study assessing the efficacy of pembrolizumab (pembro) plus radiotherapy (RT) in metastatic triple negative breast cancer (mTNBC)', *Journal of Clinical Oncology*, 36: 14-14.
31. Mittendorf EA et al. (2014) 'PD-L1 expression in triple-negative breast cancer', *Cancer Immunol Res*, 2: 361-70.
32. Mittendorf E et al. (2018) 'Abstract OT2-07-03: IMpassion031: A phase III study comparing neoadjuvant atezolizumab vs placebo in combination with nab-paclitaxel-based chemotherapy in early triple-negative breast cancer (TNBC)', *Cancer Res*, 78: OT2-07.

33. Nanda R et al. (2016) 'Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study', *J Clin Oncol*, 34: 2460-7.
34. Nanda R et al. (2017) 'Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2', *Journal of Clinical Oncology*, 35: 506-06.
35. Rugo HS et al. (2018) 'Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer', *Clin Cancer Res*, 24: 2804-11.
36. Schmid P et al. (2019) 'Abstract PD5-01: KEYNOTE-173: Phase 1b multicohort study of pembrolizumab (Pembro) in combination with chemotherapy as neoadjuvant treatment for triple-negative breast cancer (TNBC)', *Cancer Res*, 79: PD5-01-PD5-01.
37. Schmid P et al. (2019) 'Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial', *Lancet Oncol*.
38. Schmid P et al. (2018) 'KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo + chemo as neoadjuvant therapy followed by pembro vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC)', *Journal of Clinical Oncology*, 36: TPS602-TPS02.
39. Siegel RL, KD Miller & A Jemal. (2019) 'Cancer statistics, 2019', *CA Cancer J Clin*, 69: 7-34.
40. Swoboda A & Nanda R. (2018) 'Immune Checkpoint Blockade for Breast Cancer', *Cancer Treat Res*, 173: 155-65.
41. Vidula N & Bardia A. (2017) 'Targeted therapy for metastatic triple negative breast cancer: The next frontier in precision oncology', *Oncotarget*, 8: 106167-68.
42. Vinayak S et al. (2019) 'Abstract PD5-02: Durability of clinical benefit with niraparib + pembrolizumab in patients with advanced triple-negative breast cancer beyond BRCA : (TOPACIO/Keynote-162)', *Cancer Res*, 79: PD5-02.
43. Vogelstein B et al. (2013) 'Cancer genome landscapes', *Science*, 339: 1546-58.
44. Wang Y, Cao S & Chen Y. (2015) 'Molecular Treatment of Different Breast Cancers', *Anticancer Agents Med Chem*, 15: 701-20.