Bölüm
24

HEPATOSELÜLER KARSİNOMDA İMMÜNOTERAPİ

Selami BAYRAM[1]

GİRİŞ

Hepatoselüler karsinom (HCC),dünya genelinde yetişkin erkeklerde 5. Sıklıkta, kadınlarda ise 9. Sıklıkta en sık tanı alan kanser türüdür.(1) HCC ayrıca dünyada kanserden ölümün en sık 4. nedenidir (2). Yüksek insidansa sahip Kuzey-Doğu Asya ve Afrika ülkelerinde sıklığı Hepatit B'ye yönelik etkin aşılama programları sayesinde artmaz iken, Amerika ve Avrupa'da insidansı ve ölüm hızı geçen 30-40 yıl içinde iki katına çıkmıştır (3). Bu gözlemler HCC'un özellikle Amerika ve Avrupa'da büyük bir sağlık sorunu olduğu ve mortalitesi yüksek bu hastalık için yeni tedavi yöntemlerinin geliştirilmesine ihtiyaç duyulduğunu göstermektedir. HCC genellikle hepatit B ve C zemininde gelişen kronik karaciğer hastalığına ikincil olarak gelişir (4) ve sıklıkla kür şansı olmayan lokal ileri ve metastatik evrelerde karşımıza çıkmaktadır. Tedavisi hastalığın evresine göre değişkenlik göstermektedir. Erken evre hastalıkta cerrahi standart tedavi yöntemidir ve 5 yıllık ortalama sağ kalım %70 civarındadır. Cerrahi veya karaciğer transplantasyonu uygulanabilir olmadığında, bölgesel tedaviler (radyofrekans, termal ve termal olmayan ablasyon ve transarteriyel kemoembolizasyon, radyoembolizasyon) oldukça değişken 3-5 yıllık sağ kalım oranları ile ikinci bir tedavi grubunu oluşturur (5,6). İleri evre rezeke edilebilir olmayan HCC'da, onaylanmış sistemik tedaviler, birinci basamakta multi kinaz tirozin kinaz inhibitörleri (mTKİ) olan sorafenib ve vasküler endotelyal büyüme faktörü (VEGF) reseptörü 1,2,3 inhibitörü lenvatinib, ikinci basamakta ise yine multi tirozin kinaz inhibitörleri olan regorafenib ve cabozantinib ve bir VEGF reseptörü monoklonal antikoru olan ramicirumab'tır. Bununla birlikte, bu tür sistemik tedaviler sadece çok sınırlı bir sağkalım yararı sağlamak-

[1] Uz. Dr., Sağlık Bilimleri Üniversitesi Antalya Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji, drselamibayram@gmail.com

KAYNAKÇA

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136:E359.
2. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol 2017; 3:1683.
3. Jemal A et al.: Annual report to the nation on the status of cancer, 1975–2014, featuring survival. J Natl Cancer Inst 2017; 109(9).
4. El-Serag H. Epidemiology of viral Hepatitis and Hepatocellular Carcinoma. Gastroenterology 2012;142:1264–1273.
5. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial emboli-sation or chemoembolisation versus symptomatic treatment in patients withunresectable hepatocellular carcinoma: a randomised controlled trial. Lancet2002;359:1734–9.
6. Llovet JM, Bruix J. Systematic review of randomized trials for unresectablehepatocellular carcinoma: chemoembolization improves survival. Hepatol-ogy 2003;37:429–42.
7. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib inadvanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90.
8. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib forpatients with hepatocellular carcinoma who progressed on sorafenib treat-ment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3trial. Lancet 2017;389:56–66.
9. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinibversus sorafenib in first-line treatment of patients with unresectable hep-atocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet2018;391:1163–73.
10. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282–296. doi:10.1016/S1470-2045(18)30937-9
11. Eatrides J, Wang E, Kothari N, Kim R. Role of systemic therapy and future directions for hepatocellular carcinoma. Cancer Control 2017;24,1073274817729243.
12. Brandi G, de RF, Agostini V, di GS, Andreone P, Bolondi L, et al. Metronomic capecitabine in advanced hepatocellular carcinoma patients: a phase II study.Oncologist 2013;18:1256–7.
13. Ballardini P, Marri I, Margutti G, Aliberti C, Benea G, Manfredini R. Long-lasting response with metronomic capecitabine in advanced hepatocellularcarcinoma. Tumori 2010;96:768–70
14. Pardee AD, Butterfield LH. Immunotherapy of hepatocellular carci-noma: unique challenges and clinical opportunities. Oncoimmunology2012;1:48–55.
15. Kapanadze T, Gamrekelashvili J, Ma C, Chan C, Zhao F, Hewitt S, et al.Regulation of accumulation and function of myeloid derived suppressorcells in different murine models of hepatocellular carcinoma. J Hepatol2013;59:1007–13.
16. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502. doi:10.1016/S0140-6736(17)31046-2
17. Yau, T.; Park, J.W.; Finn, R.S.; Cheng, A.; Mathurin, P.; Edeline, J.; Kudo, M.; Han, K.; Harding, J.J.; Merle, P.; et al. CheckMate 459: A Randomized, Multi-Center Phase 3 Study of Nivolumab (NIVO) vs. Sorafenib (SOR) as First-Line (1L) Treatment in Patients (pts) With Advanced Hepatocellular Carcinoma (aHCC). Ann. Oncol. 2019, 30, v851–v934.
18. Zhu AX, Finn RS, Cattan S. KEYNOTE-224: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. J Clin Oncol 2018;36(suppl 4S):abstr 209.
19. Finn, R.S.; Ryoo, B.-Y.; Merle, P.; Kudo, M.; Bouattour, M.; Lim, H.-Y.; Breder, V.V.; Edeline, J.; Chao, Y.; Ogasawara, S.; et al. Results of KEYNOTE-240: Phase 3 study of pembrolizumab

(Pembro) vs. best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J. Clin. Oncol. 2019, 37, 4004.
20. Wainberg, Z.A.; Segal, N.H.; Jaeger, D.; Lee, K.-H.; Marshall, J.; Antonia, S.J.; Butler, M.; Sanborn, R.E.; Nemunaitis, J.J.; Carlson, C.A.; et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). J. Clin. Oncol. 2017, 35, 4071.
21. Wainberg ZA, Segal NH, Jaeger D, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). J Clin Oncol 2017;35(15_suppl):4071.
22. Lee, M.; Ryoo, B.; Hsu, C.; Numata, K.; Stein, S.; Verret,W.; Hack, S.; Spahn, J.; Liu, B.; Abdullah, H.; et al. Randomised E_cacy and Safety Results for Atezolizumab (Atezo) + Bevacizumab (Bev) in Patients (pts) with Previously Untreated, Unresectable Hepatocellular Carcinoma (HCC). Ann. Oncol. 2019, 30, v851–v934.
23. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol*. 2013;59(1):81–88. doi:10.1016/j.jhep.2013.02.022
24. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018 Nov;19:1480-1492.
25. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378:1277-1290.
26. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol. 2018 Mar 10;36:773-779.
27. Kim R, Keam B, Hahn S, et al. First-line Pembrolizumab Versus Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone in Non-small-cell Lung Cancer: A Systematic Review and Network Meta-analysis. Clin Lung Cancer. 2019 May 11. pii: S1525-730430113-5.
28. Wei, S.C.; Du_y, C.R.; Allison, J.P. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov. 2018, 8, 1069–1086.
29. Buchbinder, E.I.; Desai, A. CTLA-4 and PD-1 Pathways: Similarities, Di_erences, and Implications of Their Inhibition. Am. J. Clin. Oncol. 2016, 39, 98–106.
30. Granier, C.; De Guillebon, E.; Blanc, C.; Roussel, H.; Badoual, C.; Colin, E.; Saldmann, A.; Gey, A.; Oudard, S.; Tartour, E. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. ESMO Open 2017, 2, e000213.
31. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Rutkowski, P.; Grob, J.J.; Cowey, C.L.; Lao, C.D.; Wagsta_, J.; Schadendorf, D.; Ferrucci, P.F.; et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N. Engl. J. Med. 2017, 377, 1345–1356.
32. Yau, T.; Kang, Y.-K.; Kim, T.-Y.; El-Khoueiry, A.B.; Santoro, A.; Sangro, B.; Melero, I.; Kudo, M.; Hou, M.-M.; Matilla, A.; et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. J. Clin. Oncol. 2019, 37, 4012.
33. Kelley, R.K.; Abou-Alfa, G.K.; Bendell, J.C.; Kim, T.-Y.; Borad, M.J.; Yong, W.-P.; Morse, M.; Kang, Y.-K.; Rebelatto, M.; Makowsky, M.; et al. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): Phase I safety and e_cacy analyses. J. Clin. Oncol. 2017, 35, 4073.
34. Abou-Alfa, G.K.; Chan, S.L.; Furuse, J.; Galle, P.R.; Kelley, R.K.; Qin, S.; Armstrong, J.; Darilay, A.; Vlahovic, G.; Negro, A.; et al. A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. J. Clin. Oncol. 2018, 36, TPS4144.
35. Jain, R.K. Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. Cancer Cell 2014, 26, 605–622.
36. Hanahan, D.;Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674.

37. Motz, G.T.; Coukos, G. The parallel lives of angiogenesis and immunosuppression: Cancer and other tales. Nat. Rev. Immunol. 2011, 11, 702–711.
38. Datta, M.; Coussens, L.M.; Nishikawa, H.; Hodi, F.S.; Jain, R.K. Reprogramming the Tumor Microenvironment to Improve Immunotherapy: Emerging Strategies and Combination Therapies. Am. Soc. Clin. Oncol. Educ. Book 2019, 39, 165–174.
39. Hansen, W.; Hutzler, M.; Abel, S.; Alter, C.; Stockmann, C.; Kliche, S.; Albert, J.; Sparwasser, T.;Sakaguchi, S.; Westendorf, A.M.; et al. Neuropilin 1 deficiency on CD4+Foxp3+ regulatory T cells impairs mouse melanoma growth. J. Exp. Med. 2012, 209, 2001–2016.
40. Shrimali, R.K.; Yu, Z.; Theoret, M.R.; Chinnasamy, D.; Restifo, N.P.; Rosenberg, S.A. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the e_ectiveness of adoptive immunotherapy of cancer. Cancer Res. 2010, 70, 6171–6180.
41. Shigeta, K.; Datta, M.; Hato, T.; Kitahara, S.; Chen, I.X.; Matsui, A.; Kikuchi, H.; Mamessier, E.; Aoki, S.; Ramjiawan, R.R.; et al. Dual Programmed Death Receptor-1 and Vascular Endothelial Growth Factor Receptor-2 Blockade Promotes Vascular Normalization and Enhances Antitumor Immune Responses in Hepatocellular Carcinoma. Hepatology 2019.
42. Cheng, A.-L.; Qin, S.; Ikeda, M.; Galle, P.; Ducreux, M.; Zhu, A.; Kim, T.-Y.; Kudo, M.; Breder, V.; Merle, P.; et al. Abstract LBA3—IMbrave150: E_cacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs. sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann. Oncol. 2019, 30.
43. Llovet, J.M.; Ricci, S.; Mazzaferro, V.; Hilgard, P.; Gane, E.; Blanc, J.F.; de Oliveira, A.C.; Santoro, A.; Raoul, J.L.; Forner, A.; et al. Sorafenib in advanced hepatocellular carcinoma. N. Engl. J. Med. 2008, 359, 378–390.
44. Wilhelm, S.M.; Adnane, L.; Newell, P.; Villanueva, A.; Llovet, J.M.; Lynch, M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol. Cancer Ther. 2008, 7, 3129–3140.
45. Ko, J.S.; Rayman, P.; Ireland, J.; Swaidani, S.; Li, G.; Bunting, K.D.; Rini, B.; Finke, J.H.; Cohen, P.A. Direct and di_erential suppression of myeloid-derived suppressor cell subsets by sunitinib is compartmentally constrained. Cancer Res. 2010, 70, 3526–3536.
46. 164. Xin, H.; Zhang, C.; Herrmann, A.; Du, Y.; Figlin, R.; Yu, H. Sunitinib inhibition of Stat3 induces renal cell carcinoma tumor cell apoptosis and reduces immunosuppressive cells. Cancer Res. 2009, 69, 2506–2513.
47. 65. Ozao-Choy, J.; Ma, G.; Kao, J.; Wang, G.X.; Meseck, M.; Sung, M.; Schwartz, M.; Divino, C.M.; Pan, P.Y.; Chen, S.H. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. Cancer Res. 2009, 69, 2514–2522.
48. Wang, Q.; Yu, T.; Yuan, Y.; Zhuang, H.; Wang, Z.; Liu, X.; Feng, M. Sorafenib reduces hepatic infiltrated regulatory T cells in hepatocellular carcinoma patients by suppressing TGF-beta signal. J. Surg. Oncol. 2013, 107, 422–427.
49. Mustjoki, S.; Ekblom, M.; Arstila, T.P.; Dybedal, I.; Epling-Burnette, P.K.; Guilhot, F.; Hjorth-Hansen, H.; Hoglund, M.; Kovanen, P.; Laurinolli, T.; et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. Leukemia 2009, 23, 1398–1405.
50. Rusakiewicz, S.; Semeraro, M.; Sarabi, M.; Desbois, M.; Locher, C.; Mendez, R.; Vimond, N.; Concha, A.; Garrido, F.; Isambert, N.; et al. Immune infiltrates are prognostic factors in localized gastrointestinal stromal tumors. Cancer Res. 2013, 73, 3499–3510.
51. 169. Kwilas, A.R.; Donahue, R.N.; Tsang, K.Y.; Hodge, J.W. Immune consequences of tyrosine kinase inhibitors that synergize with cancer immunotherapy. Cancer Cell Microenviron. 2015, 2.
52. Vanneman, M.; Drano_, G. Combining immunotherapy and targeted therapies in cancer treatment. Nat. Rev. Cancer 2012, 12, 237–251.
53. Kelley, R.K.; Cheng, A.-L.; Braiteh, F.S.; Park, J.-W.; Benzaghou, F.; Milwee, S.; Borgman, A.; El-Khoueiry, A.B.; Kayali, Z.K.; Zhu, A.X.; et al. Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with atezolizumab (A) versus sorafenib (S) in patients (pts) with advanced

hepatocellular carcinoma (aHCC) who have not received previous systemic anticancer therapy. J. Clin. Oncol. 2019, 37, TPS4157.

54. Ikeda, M.; Sung, M.W.; Kudo, M.; Kobayashi, M.; Baron, A.D.; Finn, R.S.; Kaneko, S.; Zhu, A.X.; Kubota, T.; Kralijevic, S.; et al. Abstract CT061: A Phase Ib trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC): Updated results. Cancer Res. 2019, 79, CT061.
55. Llovet, J.M.; Kudo, M.; Cheng, A.-L.; Finn, R.S.; Galle, P.R.; Kaneko, S.; Meyer, T.; Qin, S.; Dutcus, C.E.; Chen, E.; et al. Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): Phase 3 LEAP-002 study. J. Clin. Oncol. 2019, 37, TPS4152.
56. Kudo, M.; Motomura, K.; Wada, Y.; Inaba, Y.; Sakamoto, Y.; Kurosaki, M.; Umeyama, Y.; Kamei, Y.; Yoshimitsu, J.; Fujii, Y.; et al. First-line avelumab + axitinib in patients with advanced hepatocellular carcinoma: Results from a phase 1b trial (VEGF Liver 100). J. Clin. Oncol. 2019, 37, 4072