BÖLÜM 37

Kolon Kanserinde Adjuvan Kemoterapi

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Giriş

Kolorektal kanser (KRK) kadın ve erkeklerde en sık karşılaşılan üçüncü kanser türüdür. Kolon kanseri teşhisi konan kişilerin %20'sinde tanı anında metastaz saptanırken, %40'ında ise daha önce tedavi edilen lokalize hastalıktan sonra nüks görülmektedir. Rezeke edilemeyen metastatik KRK'nın 5 yıllık sağkalım oranı %20'nin altındadır (1). Patolojik ve moleküler testleri kullanarak geliştirilen yeni tedavi stratejileri prognozu iyileştirme potansiyeline sahiptir.

Klinik Prezentasyon

Metastatik KRK'lı hastalar kolondaki primer tümörün yerleşim yerine göre intestinal semptomlarla (embriyolojik olarak hindguttan köken alan sol kolon yerleşimli tümörler barsak alışkanlığında değişme, rektal kanama, intestinal obstrüksiyon, rektum tümörleri bunlara ilave olarak tenezm, pelvik ağrılar, embriyolojk olarak midguttan köken alan sağ kolon yerleşimli tümörler genellikle asemptomatik olup, dışkıda gizli kan pozitifliği ve anemi, karın ağrısı), metastaz bölgesine göre semptomlarla (karaciğer metastazlarına bağlı sağ üst kadran ağrısı, ileri dönemde sarılık, periton metastazlarına bağlı asit, kemik metastazlarına bağlı kemik ağrıları) ile başvururlar (1, 2, 3). Ortalama tanı yaşı 67'dir. Hastaların %12'si 50 yaşın altında olmasına rağmen son yıllarda 50 yaşın altında kolon kanseri görülme sıklığı yılda %2 oranında artmaktadır. Bu artışın nedeni tam olarak anlaşılamamakla birlikte; obezite, sedanter yaşam ve işlenmiş gıda tüketiminin sorumlu olabileceği düşünülmektedir (4, 5).

Metastatik KRK, önceden tedavi edilmiş lokalize bir KRK'nin (metastatik olmayan veya evre I-III) uzak bir bölgede tekrar nüks

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Kaynaklar

1. National Cancer Institute Surveillance. (2020). Epidemiology, and End Results Program. Cancer stat facts: colorectal cancer. 12/11/2021 tarihinde https://cancercontrol.cancer.gov/publications-data/dccps-public-data-sets-analyses/seer-statistics adresinden ulaşılmıştır.
2. Moreno CC, Mittal PK, Sullivan PS, et al. Colorectal cancer initial diagnosis: screening colonoscopy, diagnostic colonoscopy, or emergent surgery, and tumor stage and size at initial presentation. Clin Colorectal Cancer. 2016;15:67-73.
3. Ulanja MB, Rishi M, Beutler BD, et al. Colon cancer sidedness, presentation, and survival at different stages. J Oncol. 2019;2019:4315032.
4. Liu PH, Wu K, Ng K, et al. Association of obesity with risk of early-onset colorectal cancer among women. JAMA Oncol. 2019;5:37-44.
5. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol. 2017;18:e457-e471.
6. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016;6:29765.
7. National Cancer Institute SEER. (2020). Cancer Statistics Review 1975-2016. 12/11/2021 tarihinde https://seer.cancer.gov/archive/csr/1975_2016/ adresinden ulaşılmıştır.
8. National Comprehensive Cancer Network. (2021). Colon cancer. 20/11/2021 tarihinde https://www.nccn.org/ adresinden ulaşılmıştır.
9. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2017;26:404-412.
10. Moreira L, Balaguer F, Lindor N, et al. EPICOLON Consortium. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012;308:1555-1565.
11. Husain H, Velculescu VE. Cancer DNA in the circulation: the liquid biopsy. JAMA. 2017;318:1272-1274.
12. Hao YX, Fu Q, Guo YY, et al. Effectiveness of circulating tumor DNA for detection of KRAS gene mutations in colorectal cancer patients: a meta-analysis. Onco Targets Ther. 2017;10:945-953.
13. National Comprehensive Cancer Network. (2020). Rectal cancer. 20/11/2021 tarihinde https://jnccn.org/ adresinden ulaşılmıştır.
14. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25:1670-1676.
15. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11:38-47.
16. Primrose J, Falk S, Finch-Jones M, et. al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 2014;15:601-611.
17. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015;16:1306-1315.
18. Venook AP, Niedzwiecki D, Lenz H-J, et al. Effect of First-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017;317:2392-2401.
19. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34:3504.
20. Nitsche U, Stögbauer F, Späth C, et al. Right sided colon cancer as a distinct histopathological subtype with reduced prognosis. Dig Surg. 2016;33:157-163.
21. Modest DP, Ricard I, Heinemann V, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol. 2016;27:1746-1753
22. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-413.
23. Guo Y, Xiong BH, Zhang T, et al. XELOX vs. FOLFOX in metastatic colorectal cancer: an updated meta-analysis. Cancer Invest. 2016;34:94-104.
24. Yamazaki K, Nagase M, Tamagawa H, et al. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Ann Oncol. 2016;27:1539-1546.
25. Baraniskin A, Buchberger B, Pox C, et al. Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: a systematic review and meta-analysis. Eur J Cancer. 2019;106:37-44.
26. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer. 2012;12:89.
27. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. J Clin Oncol. 2008;26:3523-3529.

28. Sclafani F, Cunningham D. Bevacizumab in elderly patients with metastatic colorectal cancer. J Geriatr Oncol. 2014;5:78-88.
29. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(7):1346-1355.
30. Van Cutsem E, Lang I, Folprecht G, et al. (2010). Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial. *ASCO 2010 Gastrointestinal Cancers Symposium*, January 2010 Orlando, USA. (Abstract No: 281).
31. Bokemeyer C, Van Cutsem E, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer. 2012;48:1466-75.
32. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1065-1075.
33. Rivera F, Karthaus M, Hecht JR, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. Int J Colorectal Dis. 2017;32:1179-1190.
34. Wang ZX, Wu HX, He MM, et al. Chemotherapy with or without anti-EGFR agents in left- and right-sided metastatic colorectal cancer: an updated meta-analysis. J Natl Compr Canc Netw. 2019;17:805-811.
35. Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst. 2011;103:21-30.
36. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371:1609-1618.
37. Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer: retrospective analysis of the TRIBE trial by GONO. Ann Oncol. 2018;29:1528-1534.
38. Mattison LK, Fourie J, Desmond RA, Modak A, et al. Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African-Americans compared with Caucasians. Clin Cancer Res. 2006;12:5491-5495.
39. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther. 2018;103:210-216.
40. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22:23-30.
41. André T, Shiu K-K, Kim TW, et al. KEYNOTE-177 Investigators. Pembrolizumab in microsatelliteinstability-high advanced colorectal cancer. N Engl J Med. 2020;383:2207-2218.
42. Hecht JR. Gastrointestinal toxicity or irinotecan. Oncology (Williston Park). 1998;12:72-78.
43. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15:569-579.
44. Tabernero J, Yoshino T, Cohn AL, et al. RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16:499-508.
45. Van Cutsem E, Joulain F, Hoff PM, et al. Aflibercept plus FOLFIRI vs placebo plus FOLFIRI in second-line metastatic colorectal cancer: a post hoc analysis of survival from the phase III VELOUR study subsequent to exclusion of patients who had recurrence during or within 6 months of completing adjuvant oxaliplatin-based therapy. Target Oncol. 2016;11:383-400.
46. Chau I, Joulain F, Iqbal SU, Bridgewater J. A VELOUR post hoc subset analysis: prognostic groups and treatment outcomes in patients with metastatic colorectal cancer treated with aflibercept and FOLFIRI. BMC Cancer. 2014;14:605.
47. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499-3506.
48. Tabernero J, Van Cutsem E, Lakomý R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. Eur J Cancer. 2014;50:320-331.
49. Folprecht G, Pericay C, Saunders MP, et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. Ann Oncol. 2016;27:1273-1279.
50. Cantwell-Dorris ER, O'Leary JJ, Sheils OM. BRAFV600E: implications for carcinogenesis and molecular therapy. Mol Cancer Ther. 2011;10:385-394.
51. Cohen R, Cervera P, Svrcek M, et al. BRAF-mutated colorectal cancer: what is the optimal strategy for treatment? Curr Treat Options Oncol. 2017;18:9.
52. Kambara T, Simms LA, Whitehall VL, et al. BRAF mutation is associated with DNA methylation in

serrated polyps and cancers of the colorectum. Gut. 2004;53:1137-1144.
53. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019;381:1632-1643.
54. Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAFV600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol. 2021;39:273-284.
55. Shulman K, Barnett-Griness O, Friedman V, et al. Outcomes of chemotherapy for microsatellite instable-high metastatic colorectal cancers. JCO Precis Oncol. 2018;2:2.
56. Goldstein J, Tran B, Ensor J, et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). Ann Oncol. 2014;25(5):1032-1038.
57. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (checkmate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18:1182-1191.
58. 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;36:773-779.
59. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164.J Clin Oncol. 2020;38:11-19.
60. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509-2520.
61. Thompson JA, Schneider BJ, Brahmer J, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. J Natl Compr Canc Netw. 2020;18:230-241.
62. Eng C, Kim TW, Bendell J, et al. IMblaze370 Investigators. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2019;20:849-861.
63. Ebert PJR, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity. 2016;44:609-621.
64. Ruiz-Saenz A, Dreyer C, Campbell MR, Steri V, et al. HER2 amplification in tumors activates PI3K/Akt signaling independent of HER3. Cancer Res. 2018;78:3645-3658.
65. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17:738-746.
66. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (Mypathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20:518-530.
67. Grothey A, Van Cutsem E, Sobrero A, et al. CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303-312.
68. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol. 2019;20:1070-1082.
69. Mayer RJ, Van Cutsem E, Falcone A, et al. RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372:1909-1919.
70. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013-9. doi: 10.1200/JCO.2007.14.9930.
71. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42. doi: 10.1056/NEJMoa032691.
72. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25(30):4779-86. doi: 10.1200/JCO.2007.11.3357.
73. Qin S, Li J, Wang L, et al. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. J Clin Oncol. 2018;36(30):3031-3039. doi: 10.1200/JCO.2018.78.3183.
74. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFIStudy (AIO KRK0109). J Clin Oncol. 2019;37(35):3401-3411. doi: 10.1200/JCO.19.01340.
75. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44. doi: 10.1200/JCO.2006.09.6305.
76. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14(1):29-37. doi: 10.1016/S1470-2045(12)70477-1.

77. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol. 2021:JCO2101015. doi:10.1200/JCO.21.01015.
78. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2021;22(6):779-789. doi: 10.1016/S1470 2045(21)00086-3.