



BÖLÜM 40

Gastrointestinal Stromal Tümörlerde Sistemik Tedaviler

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Giriş

Gastrointestinal stromal tümörler (GİST), çoğunlukla KIT (Tirozin kinaz reseptörü) veya PDGFRA (Platelet derive büyümeye faktör reseptör alfa) genlerinde aktive edici mutasyonlarla birlikte olan gastrointestinal sistem kanserlerinin %1-2'sini oluşturan nadir mezenkimal neoplazmlardır (1).

GİST'ler tipik olarak midede (%60) ve ince bağırsakta (%30) subepitelyal neoplazmalar olarak bulunur; bununla birlikte, gastrointestinal sistemin herhangi bir bölümünde, duodenumda (%4-5), rektumda (%4) ve çok nadiren de omentum, mezenter ve peritonda ortaya çıkabilirler (2-6).

GİST'ler ağırlıklı olarak yaşlı erişkinlerde görülür ve medyan tanı yaşı 65-69 arasındadır (7-11). GİST'ler 40 yaşın altında nadiren görülür (7).

Biyopsi ve Patolojik Değerlendirme

GİST'ler yumuşak ve kırılgan tümörlerdir. Biyopsi alma yönteminde karar, şüphelenilen tümör tipine ve hastalığın yaygınlığına göre verilmelidir. Preoperatif tedaviye başlamadan önce primer GİST tanısını doğrulamak için biyopsi gereklidir (12). Son klavuzlar, GİST'in kesin tanısının endoskopik ultrason (EUS) kılavuzlığında İİAB (İnce igne aspirasyon biyopsisi) yoluyla doku alımını gerektirdiğini ileri sürmektedir. Tümörün kanama riski ve karın içi tümör yayılımı riski perkutan biyopsiyle artar. Dolayısıyla İİAB (EUS eşliğinde) perkutan biyopsiden üstünür, İİAB tercih edilir. Perkutan görüntü kılavuzlığında biyopsi, metastatik hastalığın doğrulanması için uygun olabilir (13).

Yeterli tümör dokusunun dikkatli mikroskopik incelemesine dayanan morfolojik tanı,

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davisine yanıt veren veya sadece fokal progresyonu olan hastalara önerilmelidir. TKİ tedavisi sırasında yaygın hastalık progresyonu olan hastalar cerrahiden çok az fayda görür.

Sonuç olarak sitoredüktif cerrahi genellikle gastrektomi, hepatektomi ve pankreas rezeksiyonu gibi potansiyel olarak morbid prosedürler gerektirir ve multidisipliner merkezlerde gerçekleştirilmelidir. Bu hastalar rezeksiyondan sonra TKİ ile tedaviye devam etmelidir.

Anahtar Kelimeler: Gastrointestinal stromal tümörler, Mitotik indeks, Hedefe yönelik tedaviler, Tirozin kinaz inhibitörleri, İmatinib, Sunitinib, Regorafenib, Neoadjuvan, Adjuvan, Metastatik, KIT, DOG1, PDGFRA.

Kaynaklar

- Rubin BP, Fletcher JA, Fletcher CD. Molecular Insights into the Histogenesis and Pathogenesis of Gastrointestinal Stromal Tumors. *Int J Surg Pathol.* 2000;8:5-10.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001;438:1.
- Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999;30:1213-1220.
- Reith JD, Goldblum JR, Lyles RH, et al. Extragastrintestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. *Mod Pathol.* 2000;13:577-585.
- Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol.* 2004;28:889-894.
- Beltran MA, Cruces KS. Primary tumors of jejunum and ileum as a cause of intestinal obstruction: a case control study. *Int J Surg.* 2007;5:183-191.
- Soreide K, Sandvik OM, Soreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. *Cancer Epidemiol.* 2016;40:39-46.
- Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev.* 2015;24:298-302.
- Cassier PA, Ducimetière F, Lurkin A, et al. A prospective epidemiological study of new incident GISTS during two consecutive years in Rhône Alpes region: incidence and molecular distribution of GIST in a European region. *Br J Cancer.* 2010;103:165-170.
- Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era a population-based study in western Sweden. *Cancer.* 2005;103:821-829.
- Tryggvason G, Gíslason HG, Magnússon MK, et al. Gastrointestinal stromal tumors in Iceland, 1990-2003: the Icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer.* 2005;117:289-293.
- Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw.* 2010;8Suppl:S1-41.
- Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc.* 2009;70:254-261.
- National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2021, Gastrointestinal Stromal Tumors. (12/10/2021 tarihinde <http://www.nccn.org> adresinden ulaşılmıştır).
- Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol.* 2002;33:459-465.
- Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science.* 2003;299:708-710.
- Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology.* 2003;125:660-667.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med.* 2006;130:1466-1478.
- Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. *Proc Natl Acad Sci USA.* 2011;108:314-318.
- Italiano A, Chen CL, Sung YS, et al. SDHA loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors. *BMC Cancer.* 2012;12:408.
- Oudijk L, Gaal J, Korpershoek E, et al. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. *Mod Pathol* 2013;26:456-463.
- Pantaleo MA, Astolfi A, Urbini M, et al. Analysis of all subunits, SDHA, SDHB, SDHC, SDHD, of the succinate dehydrogenase complex in KIT/PDGFRA wild-type GIST. *Eur J Hum Genet.* 2014;22:32-39.
- Doyle LA, Nelson D, Heinrich MC, et al. Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumors: a comprehensive genotype-phenotype correlation study. *Histopathology* .2012;61:801-809.
- Agaram NP, Wong GC, Guo T, et al. Novel V600E BRAF mutations in imatinib-naïve and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer.* 2008;47:853-859.

25. Agaimy A, Terracciano LM, Dirnhofer S, et al. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRα wild-type gastrointestinal stromal tumours. *J Clin Pathol* 2009;62:613-616.
26. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am J Surg Pathol*. 2009;33:1401-1408.
27. Miettinen M, Sabin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52-68.
28. Miettinen M, Makhlouf H, Sabin LH, et al. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol*. 2006;30:477-489.
29. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*. 2003;21:4342-4349.
30. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRα mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer*. 2004;40:689-695.
31. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*. 2006;42:1093-1103.
32. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol*. 2008;26:5360-5367.
33. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*. 2004;364:1127-1134.
34. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol*. 2008;26:626-632.
35. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer*. 2005;41:1751-1757.
36. Guilhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist*. 2004;9:271-281.
37. Trent JC, Patel SS, Zhang J, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. *Cancer*. 2010;116:184-192.
38. Chu D, Lacouture ME, Weiner E, et al. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. *Clin Genitourin Cancer*. 2009;7:11-19.
39. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncol*. 2009;48:9-17.
40. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*. 2007;370:2011-2019.
41. Torino F, Corsello SM, Longo R, et al. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. *Nat Rev Clin Oncol*. 2009;6:219-228.
42. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol*. 2008;26:5352-5359.
43. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res*. 2005;11:4182-4190.
44. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. *J Clin Oncol*. 2006;24:4764-4774.
45. Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. *Clin Cancer Res*. 2006;12:1743-1749.
46. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. *Clin Cancer Res*. 2007;13:5398-5405.
47. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295-302.
48. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. *Ann Oncol*. 2016;27:1794-1799.
49. Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial [abstract]. *J Clin Oncol*. 2011;29(15_Suppl):Abstract 10009.
50. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. *Invest New Drugs*. 2012;30:2377-2383.

51. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. *Eur J Cancer.* 2013;49:1027-1031.
52. Kefeli U, Benekli M, Sevinc A, et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: A retrospective multicenter experience. *Oncol Lett.* 2013;6:605-611.
53. Demetri GD, Casali PG, Blay JY, et al. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. *Clin Cancer Res.* 2009;15:5910-5916.
54. Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. *Eur J Cancer.* 2009;45:2293-2297.
55. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third- line therapy for patients with gastrointestinal stromal tumor. *Cancer.* 2011;117:4633-4641.
56. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. *Ann Oncol.* 2012;23:1680-1687.
57. Cauchi C, Somaiah N, Engstrom PF, et al. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. *Cancer Chemother Pharmacol.* 2012;69:977-982.
58. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRA D842V mutation. *Clin Cancer Res.* 2008;14:5749-5758.
59. Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST) [abstract]. *J Clin Oncol.* 2011;29(15Suppl):Abstract10006.
60. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. *Ann Oncol.* 2014;25:236-240.
61. Mir O, Crochet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. *Lancet Oncol.* 2016;17:632-641.
62. Schoffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib resistant gastrointestinal stromal tumors. *Ann Oncol.* 2010;21:1990-1998.
63. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol.* 2009;99:42-47.
64. McAuliffe JC, Hunt KK, Lazar AJF, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. *Ann Surg Oncol.* 2009;16:910-919.
65. Fiore M, Palassini E, Fumagalli E, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). *Eur J Surg Oncol.* 2009;35:739-745.
66. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. *BMC Cancer.* 2011;11:72.
67. Committee ASOP, Evans JA, Chandrasekhara V, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. *Gastrointest Endosc.* 2015;82:1-8.
68. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol.* 2014;32:1563-1570.
69. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA.* 2012;307:1265-1272.
70. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. *J Clin Oncol.* . 2016;34:244-250.
71. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann Surg Oncol.* 2011.
72. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol.* 2006;24:2325-2331.
73. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol.* 2006;93:304-311.
74. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol.* 2007;14:14-24.
75. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg.* 2007;245:347-352.
76. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg.* 2007;245:341-346.
77. Sym SJ, Ryu M-H, Lee J-L, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTS). *J Surg Oncol.* 2008;98:27-33.

78. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? *Ann Oncol*. 2010;21:403-408..
79. Yeh C-N, Chen T-W, Tseng J-H, et al. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. *J Surg Oncol*. 2010;102:599-603.
80. Van Den Abbeele AD, Badawi RD, Manola J, et al. Effects of cessation of imatinib mesylate (IM) therapy in patients (pts) with IM- refractory gastrointestinal stromal tumors (GIST) as visualized by FDG- PET scanning [abstract]. *J Clin Oncol*. 2004;22(14_Supp):Abstract 3012.
81. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. *Ann Surg Oncol*. 2010;17:407-415.