Bölüm
23

GASTROİNTESTİNAL PRİMER NÖROENDOKRİN TÜMÖRLER VE MEDİKAL ONKOLOJİK TEDAVİ YAKLAŞIMI

Sinem AKBAŞ[25]

GİRİŞ

Nöroendokrin hücreler vücudun çok çeşitli bölgelerinde yaygın olarak bulunmaktadır ve çeşitli nöropeptitler ile katekolaminler sentezlemektedirler. Bu bölümde gastroenteropankreatik nöroendokrin neoplazmlara genel medikal onkolojik yaklaşım incelenecek, metastatik hastalıkları ise diğer bir bölümde anlatılacaktır.

Gastroenteropankreatik nöroendokrin neoplazmların iyi veya kötü diferansiye olmalarına göre klinik gidiş değiştiği gibi doğal olarak medikal onkolojik yaklaşım da oldukça farklılaşmaktadır. İyi diferansiye tümörler daha selim bir prognoz çizerken, kötü diferansiye nöroendokrin tümörler klinik gidiş açısından akciğerin küçük hücreli veya büyük hücreli nöroendokrin karsinomuna benzetilebilir (1).

Dünya Sağlık Örgütü (WHO)'nun 2010 sınıflamasına göre gastroenteropankreatik nöroendokrin neoplazmlar mitoz sayısı ve proliferasyon indeksi Ki-67'ye göre düşük grad (G1), orta grad (G2), yüksek grad (G3) olarak ayrılmaktadır. Düşük gradlı neoplazmlar gastroenteropankreatik nöroendokrin tümörler (GEP-NET), yüksek gradlı nöroendokrin neoplazmlar ise nöroendokrin karsinomlar olarak adlandırılmaktadır. Ayrıca 2017'de pankreas endokrin tümörleri için WHO sınıflaması güncellenmiş, ki67 indeksi >%20 olan iyi ve orta diferansiye pankreas nöroendokrin tümörleri için ayrı bir kategori oluşturulmuştur.

Grad 2 GEPNET'ler düşük gradlılarla benzer şekilde tedavi edilse de biraz daha kötü prognoza sahiptir ve yeni tedavi seçenekleri ortaya çıkmaktadır (2). Nöroendokrin karsinomlar ise hızlı progrese olur, küçük hücreli akciğer kanseri gibi platin bazlı kemoterapi ile tedavi edilir.

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Lokal ileri özofagus dışı nöroendokrin karsinomlarda kombine tedavi önerilmektedir, adjuvan veya daha çok neoadjuvan kemoterapi ve kemoradyoterapi kullanılmaktadır (73).

Metastatik evrede ilk basamak tedavi platin+etoposiddir. İlk basamak tedaviden en az 3 ay sonra nüks edenler platin duyarlı kabul edilip tekrar aynı tedavi denenebilir, bir çalışmada ikinci basamak sisplatin+etoposid ile %15 parsiyel yanıt, %27 stabil hastalık gözlenmiştir (75). Diğer ikinci basamak tedavi seçenekleri olarak temozolamid, fluroprimidinler, irinotekan ve oksaliplatin bazlı rejimler sıralanabilir.

Sindirim sistemi nöroendokrin karsinomlarında prognoz oldukça kötü olup medyan sağkalım lokalize hastalık için 38 ay, lokal ileri hastalık için 16 ay, metastatik evrede ise 5-14 aydır (70,76).

Sonuç

GEPNET'lerde metastatik evrede semptom kontrolü ve tümör progresyonunu engellemek için girişimsel işlemlerin yanı sıra çeşitli sistemik tedaviler verilmekte, nöroendokrin karsinomlarda ise her evrede sistemik kemoterapi öne çıkmaktadır. Tedavi yanıtları ve prognoz orijin alınan organ, diferansiyasyon, grada göre değişmektedir.

KAYNAKLAR

1. Ohike N, Adsay NV, La Rosa S, et al.. Mixed neuroendocrine-non-neuroendocrine neoplasms.. In: WHO Classification of Tumours of Endocrine Organs, 4th ed, Lloyd RV, Osamura RY, Kloppel G, Rosai J (Eds), IARC Press, Lyon 2017. p.238.
2. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010; 39:707.
3. Caplin M, Sundin A, Nillson O, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology 2012; 95:88.
4. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005; 12:1083.
5. Yao JC1, Hassan M, Phan A, et al One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063-72.
6. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017; 3:1335
7. Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. Am J Gastroenterol 2007; 102:1464
8. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. J Surg Oncol 2005; 89:151
9. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th ed, Edge, SB, Byrd, DR, Compton, CC, et al (Eds), Springer, New York 2010. p.181.

10. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. Neuroendocrinology 2009; 89:471.
11. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer 2011; 117:3332.
12. Landerholm K, Zar N, Andersson RE, et al. Survival and prognostic factors in patients with small bowel carcinoid tumour. Br J Surg 2011; 98:1617.
13. Kim MK, Warner RR, Roayaie S, et al. Revised staging classification improves outcome prediction for small intestinal neuroendocrine tumors. J Clin Oncol 2013; 31:3776
14. Takatsu Y, Fukunaga Y, Nagasaki T, et al. Short- and Long-term Outcomes of Laparoscopic Total Mesenteric Excision for Neuroendocrine Tumors of the Rectum. Dis Colon Rectum 2017; 60:284.
15. Mani S, Modlin IM, Ballantyne G, et al. Carcinoids of the rectum. J Am Coll Surg 1994; 179:231
16. Fahy BN, Tang LH, Klimstra D, et al. Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment. Ann Surg Oncol 2007; 14:1735
17. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97:934
18. Chagpar R, Chiang YJ, Xing Y, et al. Neuroendocrine tumors of the colon and rectum: prognostic relevance and comparative performance of current staging systems. Ann Surg Oncol 2013; 20:1170.
19. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol 2012; 19:1379.
20. Pape UF, Perren A, Niederle B, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012; 95:135
21. Landry CS, Woodall C, Scoggins CR, et al. Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. Arch Surg 2008; 143:664.
22. Borch K, Ahrén B, Ahlman H, et al Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg. 2005;242(1):64
23. Thomas D, Tsolakis AV, Grozinsky-Glasberg S, et al. Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study. Eur J Endocrinol 2013; 168:185.
24. Dakin GF, Warner RR, Pomp A, et al. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. J Surg Oncol 2006; 93:368.
25. Ferraro G, Annibale B, Marignani M, et al. Effectiveness of octreotide in controlling fasting hypergastrinemia and related enterochromaffin-like cell growth. J Clin Endocrinol Metab 1996; 81:677
26. Burkitt MD, Pritchard DM. Review article:pathogenesis and management of gastric carcinoid tumors; Aliment Pharmacol Ther. 2006 Nov 1;24(9):1305-20.
27. Gladdy RA, Strong VE, Coit D, et al. Defining surgical indications for type 1 gastric carcinoid tumour. Ann Surg Oncol 2009; 16:3154–3160
28. National Comprehensive Cancer Network (NCCN) (2019). NCCN Clinical practice guidelines in oncology. (09.07.2019 tarihinde https://www.nccn.org/professionals/physician_gls/default.aspx sitesinden erişilmiştir.).
29. Reubi JC, Kvols LK, Waser B, et al. Detection of somatostatin receptors in surgical and percutaneous needle biopsy samples of carcinoids and islet cell carcinomas. Cancer Res 1990; 50:5969.
30. Bousquet C, Lasfargues C, Chalabi M, et al. Clinical review: Current scientific rationale for the use of somatostatin analogs and mTOR inhibitors in neuroendocrine tumor therapy. J Clin Endocrinol Metab 2012; 97:727.
31. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27:4656.

32. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014; 371:224.
33. Michael M, Garcia-Carbonero R, Weber MM, et al. The Antiproliferative Role of Lanreotide in Controlling Growth of Neuroendocrine Tumors: A Systematic Review. Oncologist 2017; 22:272.
34. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012; 95:157.
35. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013; 42:557.
36. Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol 1999; 17:600.
37. Broder MS, Beenhouwer D, Strosberg JR, et al. Gastrointestinal neuroendocrine tumors treated with high dose octreotide-LAR: a systematic literature review. World J Gastroenterol 2015; 21:1945.
38. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999; 340:858.
39. Choti MA, Bobiak S, Strosberg JR, et al. Prevalence of functional tumors in neuroendocrine carcinoma: An analysis from the NCCN NET database. ASCO Meeting Abstracts 2012;30:4126.
40. Soga J, Yakuwa Y, Osaka M. Carcinoid syndrome: a statistical evaluation of 748 reported cases. J Exp Clin Cancer Res 1999;18: 133-141
41. Pasieka JL, McKinnon JG, Kinnear S, et al. Carcinoid syndrome symposium on treatment modalities for gastrointestinal carcinoid tumors: symposium summary. Can J Surg 2001;44:25-32
42. Oberg K, Kvols L, Caplin M, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004; 15:966.
43. Strosberg JR, Fisher GA, Benson AB, et al. Systemic treatment in unresectable metastatic well-differentiated carcinoid tumors: consensus results from a modified delphi process. Pancreas 2013; 42:397.
44. Strosberg JR, Benson AB, Huynh L, et al. Clinical benefits of above-standard dose of octreotide LAR in patients with neuroendocrine tumors for control of carcinoid syndrome symptoms: a multicenter retrospective chart review study. Oncologist 2014; 19:930.
45. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol 2017; 35:14.
46. Kiesewetter B, Raderer M. Ondansetron for diarrhea associated with neuroendocrine tumors. N Engl J Med 2013; 368:1947.
47. Woodside KJ, Townsend CM Jr, Mark Evers B. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg 2004; 8:742.
48. Kinney MA, Warner ME, Nagorney DM, et al. Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. Br J Anaesth 2001; 87:447.
49. Veall GR, Peacock JE, Bax ND, Reilly CS. Review of the anaesthetic management of 21 patients undergoing laparotomy for carcinoid syndrome. Br J Anaesth 1994; 72:335.
50. Warner RR, Mani S, Profeta J, Grunstein E. Octreotide treatment of carcinoid hypertensive crisis. Mt Sinai J Med 1994; 61:349.
51. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation 1993; 87:1188.
52. Roth BL. Drugs and valvular heart disease. N Engl J Med 2007; 356:6.
53. Denney WD, Kemp WE Jr, Anthony LB, et al. Echocardiographic and biochemical evaluation of the development and progression of carcinoid heart disease. J Am Coll Cardiol 1998; 32:1017.
54. Møller JE, Connolly HM, Rubin J, et al. Factors associated with progression of carcinoid heart disease. N Engl J Med 2003; 348:1005.
55. Fesinmeyer MD, Austin MA, Li CI, et al. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2005; 14:1766.

56. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008; 135:1469.
57. Kasumova GG, Tabatabaie O, Eskander MF, et al. National Rise of Primary Pancreatic Carcinoid Tumors: Comparison to Functional and Nonfunctional Pancreatic Neuroendocrine Tumors. J Am Coll Surg 2017; 224:1057
58. de Mestier L, Hentic O, Cros J, et al. Metachronous hormonal syndromes in patients with pancreatic neuroendocrine tumors: a case-series study. Ann Intern Med 2015; 162:682.
59. Toumpanakis C, Caplin ME. Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. Semin Oncol 2013; 40:56.
60. Nikou GC, Toubanakis C, Nikolaou P, et al. VIPomas: an update in diagnosis and management in a series of 11 patients. Hepatogastroenterology 2005; 52:1259.
61. Frankton S, Bloom SR. Gastrointestinal endocrine tumours. Glucagonomas. Baillieres Clin Gastroenterol 1996; 10:697.
62. Angeletti S, Corleto VD, Schillaci O, et al. Use of the somatostatin analogue octreotide to localise and manage somatostatin-producing tumours. Gut 1998; 42:792.
63. Soga J, Yakuwa Y. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. J Exp Clin Cancer Res 1999; 18:13.
64. Hirshberg B, Cochran C, Skarulis MC, et al. Malignant insulinoma: spectrum of unusual clinical features. Cancer 2005; 104:264
65. Norton JA. Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg 1994; 31:77.
66. Norton JA, Foster DS, Ito T, Jensen RT. Gastrinomas: Medical or Surgical Treatment. Endocrinol Metab Clin North Am 2018; 47:577.
67. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine (Baltimore) 2000; 79:379.
68. Basturk O, Yang Z, Tang LH, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol 2015; 39:683
69. Dasari A, Mehta K, Byers LA, et al. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. Cancer 2018; 124:807.
70. Walter T, Tougeron D, Baudin E, et al. Poorly differentiated gastro-entero-pancreatic neuroendocrine carcinomas: Are they really heterogeneous? Insights from the FFCD-GTE national cohort. Eur J Cancer 2017; 79:158.
71. La Rosa S, Sessa F, Uccella S. Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs): Unifying the Concept of a Heterogeneous Group of Neoplasms. Endocr Pathol 2016; 27:284.
72. Sorbye H, Strosberg J, Baudin E, et al. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer 2014; 120:2814.
73. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas 2010; 39:799.
74. Ku GY, Minsky BD, Rusch VW, et al. Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience. Ann Oncol 2008; 19:533.
75. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol 2013; 24:152.
76. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, November 2011 submission (1973-2010). Bethesda, MD: National Cancer Institute, Cancer Statistics Branch; 2013. www.seer.cancer.gov.