

Bölüm 15

TROİD KANSERLERİNDE TİROZİN KİNAZ İNHİBİTÖR TEDAVİSİ

Deniz IŞIK¹

GİRİŞ

Tiroid kanserleri endokrin sistemin en sık görülen malignitesi olmasına rağmen tüm kanserlerin ancak %1 den azını oluşturur(1). Yıllık insidansı 8/100.000 civarındadır(2) ve kadınlarda erkeklerden 3 kat daha fazla görülür(3). Tiroid kanserlerinin ana histolojik alt tipleri diferansiye , medüller ve anaplastik kanserlerdir. Tiroid kanserlerinde başlıca tedavi yöntemleri cerrahi, radyoaktif iyot tedavisi, radyoterapi olmasına rağmen bu tedaviler altında progresyon ve metastaz gelişen vakalarda kemoterapi kullanılır. Konvansiyonel kemoterapötiklerin düşük etkinliği nedeni ile oral tirozin kinaz inhibitörleri (TKI) tiroid kanserlerinde kemoterapinin esas ögesi olarak öne çıkmaktadır.

DİFERANSİYE TİROİD KANSERLERİ

Diferansiye tiroid kanserleri (DTK) papiller , foliküler ve Hurthle hücreli kanserleri içerir. Foliküler epitel hücrelerinden kaynaklanır ve normal tiroid dokusunun temel özelliklerine sahiptir. DTK nadir bir hastalık grubu olmasına rağmen dünya genelinde insidansı giderek artmaktadır(4). Klinikte saptanan tiroid kanserlerinin %60-80'ini mikropapiller tiroid kanseri oluşturur. Bu kanser türleri sodyum iyot simporter (NIS) ekspresyonu özelliğine sahiptir ve bu transmembran protein iyodun hücre içerisine alınmasında görev alır. Cerrahi , radyoaktif iyot tedavisi ile hastalığın prognozu genellikle çok iyidir. On yıllık sağkalım % 85'lere ulaşmasına rağmen %30'lara varan oranlarda nüks edebildiği için yakın takip çok önemlidir (5,6,7).

Kinaz inhibitörleri

Birçok kanser türünde kinaz fonksiyonu tümör büyümesi , invazyon, metastaz ve apoptozdan kaçışta anahtar rol oynar. RET/PTC füzyon proto-onkogeni, RAS, BRAF ve VEGFR'ı hedefleyen küçük molekül inhibitörler DTK tedavisinde kli-

¹ Dr. Öğr. Üyesi, Dr Ersin Arslan Eğitim ve Araştırma Hastanesi, deniz-isik@windowslive.com

Mevcut tedavilerden başka deneysel TKI tedavileri devam etmekle beraber çoğu ilacın özellikle hastalık stabilizasyonu sağlamadaki etkinlikleri ön plana çıkmaktadır.

ANAPLASTİK TİROİD KANSERİ

Tüm kanser türleri arasında en agresif seyirli olanlardandır ve ortalama sağ kalım nadiren 12 ayı aşar(7). Diferansiye tiroid kanserinin terminal dediferansasyonu ile geliştiği düşünülür. BRAF mutasyonunun patogenezdaki rolü belirlenmesine rağmen vaka sayılarındaki yetersizlik nedeniyle hedefe yönelik tedavilerden fayda sağlanamamıştır.

Imatinib : PDGFR, C-KIT ve BCR-ABL inhibisyonu sağlar. Anaplastik tümörlerde PDGFR aşırı ekspresyonu bildirilmiştir. 11 hastalık faz 2 çalışmada 2 hastada kısmi yanıt 4 hastada stabil yanıt alındı.

Sorafenib : küçük hasta gruplarında etkinlik değerlendirilmesi yapılmış ancak progresyonsuz sağ kalım bu çalışmalarda 4 ayı geçememiştir.

Crolibulin ve fosbretabulin gibi vasküler endotel hücrelerindeki tübüllerin destabilizasyonunu sağlayan ajanlar kemoterapi ile kombine denendi. Bunun haricinde BRAF , PI3K/mTOR ve MAPK sinyal yollarına yönelik deneysel ajanların çalışmaları devam etmektedir.

Bu derlemede tiroid kanserlerinin tedavisinde etkinlik göstermiş oral TKI' lara değindik. Tiroid kanserlerinin (anaplastik hariç) indolen seyri nedeni ile ve aynı zamanda kinaz inhibitörlerinin ciddi grade 3-4 yan etkileri ve hatta letal etki göstermeleri sebebi ile tedavi başlama kararı alınırken iyi düşünülmeli ve mutlaka semptomatik , hızlı progrese hastalarda bu ajanlara başvurulmalıdır.

KAYNAKLAR

1. Robie DK , Dinauer CW, Tuttle RM, Ward DT, Parry R, McClellan D, et al. The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. J Pediatr Surg 1998 ;33(7):1134-8; discussion 1139-40.
2. Biermann M, Pixberg MK, Schuck A, Heinecke A, Köpcke W, Schmid KW, et al. Multicenter study differentiated thyroid carcinoma (MSDS). Diminished acceptance of adjuvant external beam radiotherapy. Nuklearmedizin 2003;42(6):244-50
3. American Thyroid Association Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated cancer. Thyroid 2009;19(11):1167-214.
4. Tuttle RM HR, Haddad RI, Ball DW, Byrd D, Dickson P, Duh QY , et al. Thyroid carcinoma: NCCN;2014.

5. Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB. The effects of surgery, radioiodine, external beam radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. *Cancer* 1998;82(2):375-88
6. Wartofsky L. Highlights of the American Thyroid Association Guidelines for patients with thyroid nodules or differentiated thyroid carcinoma: the 2009 revision. *Thyroid* 2009;19(11):1139-43
7. Farahati J, Reiners C, Stuschke M, Müller SP, Stüben G, Sauerwien W, et al. Differentiated thyroid cancer. Impact of adjuvant external beam radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). *Cancer* 1996;77(1):172-80.
8. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 2009; 9:28.
9. Haugen BR, Sherman SI. Evolving approaches to patients with advanced differentiated thyroid cancer. *Endocr Rev* 2013; 34:439.
10. Schlumberger M, Sherman SI. Clinical trials for progressive differentiated thyroid cancer: patient selection, study design, and recent advances. *Thyroid* 2009; 19:1393.
11. Brose MS, Troxel AB, Redlinger M, et al. Effect of BRAFV600E on response to sorafenib in advanced thyroid cancer patients. *J Clin Oncol (Meeting Abstracts)* 2009; 27:6002.
12. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008; 359:31.
13. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434288.htm> (Accessed on February 13, 2015).
14. Cabanillas ME, Schlumberger M, Jarzab B, et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: A clinical outcomes and biomarker assessment. *Cancer* 2015; 121:2749.
15. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015; 372:621.
16. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014; 384:319.
17. Dubauskas Z, Kunishige J, Prieto VG, et al. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. *Clin Genitourin Cancer* 2009; 7:20.
18. Leboulleux S, Bastholt L, Krause T, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol* 2012; 13:897.
19. Cabanillas ME, de Souza JA, Geyer S, et al. Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. *J Clin Oncol* 2017; 35:3315.
20. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007; 6:2012.
21. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol* 2010; 11:962.
22. Kim DW, Jo YS, Jung HS, et al. An orally administered multitarget tyrosine kinase inhibitor, SU11248, is a novel potent inhibitor of thyroid oncogenic RET/papillary thyroid cancer kinases. *J Clin Endocrinol Metab* 2006; 91:4070.

23. Cohen EE, Needles BM, Cullen KJ, et al. Phase 2 study of sunitinib in refractory thyroid cancer. *J Clin Oncol (Meeting Abstracts)* 2008; 26.
24. Carr L, Goulart B, Martins R, et al. Phase II trial of continuous dosing of sunitinib in advanced, FDG-PET avid, medullary thyroid carcinoma (MTC) and well-differentiated thyroid cancer (WDTC). *J Clin Oncol (Meeting Abstracts)* 2009; 27:6056.
25. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol* 2008; 26:4708.
26. Brose MS, Cabanillas ME, Cohen EE, et al. Vemurafenib in patients with BRAF(-V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016; 17:1272.
27. Shah MH, Wei L, Wirth LJ, et al. Pembrolizumab for advanced papillary or follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 study. *J Clin Oncol* 2016; 34:6091.
28. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* 2013; 368:623.
29. Lim SM, Chang H, Yoon MJ, et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. *Ann Oncol* 2013;24:3089-94.
30. Wells, S. A. Jr et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the american thyroid association guidelines task force on medullary thyroid carcinoma. *Thyroid* 2015;25:567-610(2015).
31. Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: implications for diagnosis, treatment and prognosis. *Expert Rev Mol Diagn* 2008; 8:83.
32. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 2009; 9:28.
33. <http://www1.astrazeneca-us.com/pi/vandetanib.pdf> (Accessed on April 13, 2011).
34. Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30:134.
35. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022405s0001bl.pdf (Accessed on April 08, 2011).
36. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002315/WC500123533.pdf (Accessed on October 01, 2012).
37. <http://www.medicines.org.uk/EMC/medicine/26040/SPC/Caprelsa+100+mg+%26+300+mg+film+coated+tablets/> (Accessed on October 01, 2012).
38. US Food and Drug Administration. FDA approves Cometriq to treat rare type of thyroid cancer. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm330143.htm> (Accessed on December 03, 2012).
39. Schoffski P, Elisei R, Muller S, et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. *J Clin Oncol* 2012; 30 (suppl):5508. http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/5508 (Accessed on January 25, 2013).
40. Sherman SI, Clary DO, Elisei R, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. *Cancer* 2016; 122:3856.

41. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral anti-tumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; 64:7099.
42. Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol* 2010; 28:2323.
43. Hong DS, Sebti SM, Newman RA, et al. Phase I trial of a combination of the multi-kinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in advanced malignancies. *Clin Cancer Res* 2009; 15:7061.
44. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin Cancer Res* 2010; 16:5260.
45. Schlumberger M, Jarzab B, Cabanillas ME, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. *Clin Cancer Res* 2016; 22:44.
46. Bible KC, Suman VJ, Molina JR, et al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab* 2014; 99:1687.