Bölüm 22

ATİPİK KRONİK MİYELOİD LÖSEMİ

Sevil SADRİ[1]

Dünya Sağlık Örgütü (DSÖ) tanı kriterlerine göre atipik kronik miyeloid lösemi(aKML), daha önce sınıflandırılmayan kronik miyeloid lösemiye (KML) morfolojik benzerlik gösteren ancak standart sitogenetik ile Ph kromozomun ve polimeraz zincir reaksiyonu ile BCR-ABL1 düzenlenmesi olamayan hastalık grubudur (Arber & arkadaşları 2016).

BCR-ABL-1 negatif hematolojik neoplazmaların ayırıcı tanısında sadece KML ile değil, aynı zamanda kronik miyelomonositik lösemi (KMML), kronik nötrofilik lösemi (KNL) ve miyelodispalstik sendrom/ miyeloproliferatif neoplazm ile ayrıcı tanı yapılması gerekir(Vardiman & arkadaşları 2008). aKML tanı zorlukları, heterojen klinik ve genetik özellikleri, akut miyeloid lösemiye yüksek oranda dönüşüm ve kötü prognoz sebebi ile uygun donörü olan hastalar için allojenik hematopoetik kök hücre nakli her zaman uygun bir tercihtir (Gotlib & arkadaşları 2013a).

TANI KRİTERLERİ

Geçmişte aKML vakaları, KML benzeri sendrom olarak adlandırılırdı. Günümüzde ise yapılan çalışmalar sonunda aKML olarak isimlendirilmiş ve tanı kriterleri DSÖ tarafından belirlenmiştir. (Tablo-1)

Bir İtalyan kohortunda, 55 aKML olgusu incelenmiş; hastaların medyan sağkalım süreleri 14 ile 30 ay olarak raporlanmıştır (Breccia & arkadaşları 2013). Yakın zamanda Amerika birleşik devletlerinde(ABD) yapılan çok merkezli bir çalışmada aKML(n=65) ve MDS/MPN,U (n=69) vakalarını karşılatırılmış, DSÖ kriterlerini uygulanmış ve önceki medyan sağkalımlarıyla daha agresif bir klinik seyir sergilediği tespit edilmiştir (12.4 ve 21.8 ay) (Gotlib & arkadaşları 2013b). ABD ve Italyan çalışmalarında, akut miyeloid lösemiye dönüşüm sırasıyla vakaların %37 ve %40 ‘ında gerçekleşmiş ve ortalama dönüşüm süresi 11.2 ve 18 ay olarak izlenmiştir(Wang & arkadaşları 2014).

[1] Uzm. Dr., Medipol Mega Üniversitesi, sevilsadri@hotmail.com

RA pozitif bir hastada eozinofilleri azaltmıştır. HES terapisinde kullanılan diğer ilaçlar alemtuzumab(Dearden & arkadaşları 2009) ve infliksimabdır(Taverna & arkadaşları, 2007) yakın zamanda, glukokortikoid, hidroksikarbamid, imatinib, mepolizumab gibi mevcut tedavi seçeneklerinin başarısız olduğu ve interferon A'ya kısmi yanıt veren bir hastada alemtuzumab kullanılmıştır. Alemtuzumab, periferik kan eozinofiliyi minimal toksisite ile çarpıcı şekilde düşürmüştür(Wagner & arkadaşları, 2009) . Eritroderma ile başvuran tanımsız / kompleks varyan HES olan bir hasta infliximab'a cevap vermiştir (Taverna & arkadaşları, 2007). Eozinofilik hastalıkların hücresel ve moleküler özelliklerinin daha iyi anlaşılmasıyla, biyolojik olarak daha anlamlı, tedavi belirlemede işe yarayan, sınıflandırma şemaları geliştirilmiştir. Daha önce HES grubu içinde yer alan ve kötü prognoza sahip pek çok hasta artık imatinib ve diğer yeni ajanlarla tedavi edilebilmektedi.

KAYNAKÇA

Ault, P., Cortes, J., Koller, C., Kaled, E.S. & Kantarjian, H. (2002) Response of idiopathic hypereosinophilic syndrome to treatment with imatinib mesylate. *Leukemia Research*, 26, 881–884.

Bae, S.Y., Yoon, S.Y., Huh, J.H., Sung, H.J. & Choi, I.K. (2007) Hypereosinophilia in biphenotypic (B-cell/T-cell) acute lymphoblastic leukemia. *Leukaemia & Lymphoma*, 48, 1417–1419.

Barge, S., Bouchachi, A., Bechara, C., Lazure, T., Assayag, P. & Lambotte, O. (2008) Eosinophilia with stroke in a Chinese patient: Kimura's disease complicated with fibroblastic endocarditis, first report. *American Journal of Hematology*, 83, 432.

Becker, V., Lersch, C., Gaa, J. & Schmid, R.M. (2006) Partial Budd-Chiari syndrome associated with a hypereosinophilic syndrome. *Zeitschrift fur Gastroenterologie*, 44, 173–177.

Bogenrieder, T., Griese, D.P., Schiffner, R., Buttner, R., Riegger, G.A., Hohenleutner, U. & Landthaler, M. (1997) Wells' syndrome associated with idiopathic hypereosinophilic syndrome.*British Journal of Dermatology*, 137, 978–982.

Butterfield, J.H. (2001) Diverse clinical outcomes of eosinophilic patients with T-cell receptor gene rearrangements: the emerging diagnostic importance of molecular genetics testing. *American Journal of Hematology*, 68, 81–86.

Caldwell JM, Collins MH, Stucke EM, et al. (2014)Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, Th2 immunity and a unique gastric transcriptome *J Allergy Clin Immunol*.

Chen J, DeAngelo DJ, Kutok JL, et al. (2004)PKC412 inhibits the zinc finger 198- fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. Proc Natl Acad Sci USA 101:14479–14484.

Chusid MJ, Dale DC, West BC, Wolff SM. (1975)The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) .54(1):1–27.

Chusid, M.J., Dale, D.C., West, B.C. & Wolff, S.M. (1975) The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)*, 54, 1–27.

Dao KH, Solti MB, Maxson JE, et al. (2014)Significant clinical response to JAK1/2

inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid leukemia. Leuk Res Rep. 3(2):67-69.

Dao KH, Solti MB, Maxson JE, et al. (2014)Significant clinical response to JAK1/2 inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid leukemia. *Leuk Res Rep.* **3**(2):67–69.

Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH.(2014) Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. Allergy. 2014;69(2):269–272.

Gleich GJ, Schroeter AL, Marcoux JP, Sachs MI, O'Connell EJ, Kohler PF. (1984)Episodic angioedema associated with eosinophilia. N Engl J Med. 310(25):1621–1626.

Gotlib J, Maxson JE, George TI, Tyner JW. (2013)The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood. 122(10):1707-1711.

Gotlib J. (2017)How I treat atypical chronic myeloid leukemia. Blood. 129(7):838-845

Greenhawt M, Aceves SS, Spergel JM, Rothenberg ME. (2013)The management of eosinophilic esophagitis. J Allergy Clin Immunol Pract. 1(4):332–340, quiz 341-342.

Irgang S, Ultmann R. (1949)Mycosis fungoides with intense eosinophilia. Harlem Hosp Bull (N Y) .2(1):34–41

Klion AD, Bochner BS, Gleich GJ, et al. (2006)The Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol. 117(6):1292–1302.

Kurzrock R, Kantarjian HM, Shtalrid M, Gutterman JU, Talpaz M. (1990)Philadelphia chromosome-negative chronic myelogenous leukemia without breakpoint cluster region rearrangement: a chronic myeloid leukemia with a distinct clinical course. Blood. 75(2):445-452.

Lasho TL, Finke CM, Zblewski D, et al. (2015)Novel recurrent mutations in ethanolamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosinophilia and chronic myelomonocytic leukemia.Blood Cancer J. 5:e275

Lincoff, N.S. & Schlesinger, D. (2005) Recurrent optic neuritis as the presenting manifestation of primary hypereosinophilic syndrome: a report of two cases. *Journal of Neuro-Ophthalmology*, 25, 116–121.

Maxson JE, Gotlib J, Pollyea DA, et al. (2013)Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med. 368(19):1781-1790.

McMillan, H.J., Johnston, D.L. & Doja, A. (2008) Watershed infarction due to acute hypereosinophilia. *Neurology*, 70, 80–82.

Mao L, You L, Yang M, et al. (2013)The first case of decitabine successfully in treatment of atypical chronic myeloid leukemia with CEPBPA double mutation. Chemotherapy. 2:114

Martiat P, Michaux JL, Rodhain J. (1991)Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Français de Cytogénétique Hématologique. Blood. 78(1):205-211.

Ng, H.J., Tan, D.C., Yiu, R.C. & How, G.F. (2008) Maintenance therapy with imatinib appears necessary despite molecular remission in FIP1L1-PDGFRA fusion gene positive hypereosinophilic disorder. *Leukemia Research*, 32, 169–171.

Pardanani, A., Brockman, S.R., Paternoster, S.F., Flynn, H.C., Ketterling, R.P., Lasho, T.L., Ho, C.L., Li, C.Y., Dewald, G.W. & Tefferi, A. (2004) FIP1L1-PDGFRA fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood*, 104, 3038–3045.

Pardanani, A., Elliott, M., Reeder, T., Li, C.Y., Baxter, E.J., Cross, N.C. & Tefferi, A. (2003b) Imatinib for systemic mast-cell disease. *Lancet*, 362, 535–536

Pardanani, A., Ketterling, R.P., Li, C.Y., Patnaik, M.M., Wolanskyj, A.P., Elliott, M.A., Camoriano, J.K., Butterfield, J.H., Dewald, G.W. & Tefferi, A. (2006) FIP1L1-PDGFRA in eosinophilic disorders: prevalence in routine clinical practice, long-term experience with imatinib therapy, and a critical review of the literature. *Leukemia Research*, 30, 965–970

Patnaik MM, Tefferi A. (2016)Chronic myelomonocytic leukemia: 2016 update on diagnosis, risk stratification, and management. Am J Hematol.**91**(6):631-642

Piazza R, Valletta S, Winkelmann N, et al. (2013)Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. Nat Genet. 45(1):18-24

Renston JP, Goldman ES, Hsu RM, Tomashefski JFJ., Jr (2000)Peripheral blood eosinophilia in association with sarcoidosis. Mayo Clin Proc. 75(6):586–590.

Roche-Lestienne, C., Lepers, S., Soenen-Cornu, V., Kahn, J.E., Lai, J.L., Hachulla, E., Drupt, F., Demarty, A.L., Roumier, A.S., Gardembas, M., Dib, M., Philippe, N., Cambier, N., Barete, S., Libersa, C., Bletry, O., Hatron, P.Y., Quesnel, B., Rose, C., Maloum, K., Blanchet, O., Fenaux, P., Prin, L. & Preudhomme, C. (2005) Molecular characterization of the idiopathic hypereosinophilic syndrome (HES) in 35 French patients with normal conventional cytogenetics. *Leukemia*, 19, 792–798.

Rothenberg, M.E., Klion, A.D., Roufosse, F.E., Kahn, J.E., Weller, P.F., Simon, H.U., Schwartz, L.B., Rosenwasser, L.J., Ring, J., Griffin, E.F., Haig, A.E., Frewer, P.I., Parkin, J.M. & Gleich, G.J. (2008) Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *New England Journal of Medicine*, 358, 1215–1228

Roufosse, F., Cogan, E. & Goldman, M. (2007) Lymphocytic variant hypereosinophilic syndromes.*Immunology and Allergy Clinics of North America*, 27, 389–413

Sada, A., Katayama, Y., Yamamoto, K., Okuyama, S., Nakata, H., Shimada, H., Oshimi, K., Mori, M. & Matsui, T. (2007) A multicenter analysis of the FIP1L1-alphaPDGFR fusion gene in Japanese idiopathic hypereosinophilic syndrome: an aberrant splicing skipping the alphaPDGFR exon 12.*Annals of Hematology*, 86, 855–863

Sheikh, J. & Weller, P.F. (2007) Clinical overview of hypereosinophilic syndromes. *Immunology and Allergy Clinics of North America*, 27, 333–355

Simon HU, Plötz SG, Dummer R, Blaser K.(1999) Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. N Engl J Med. 341(15):1112–1120.

Simon, D. & Simon, H.U. (2007) Eosinophilic disorders. *Journal of Allergy and Clinical Immunology*, 119, 1291–1300

Taverna, J.A., Lerner, A., Goldberg, L., Werth, S. & Demierre, M.F. (2007) Infliximab as a therapy for idiopathic hypereosinophilic syndrome. *Archives of Dermatology*, 143, 1110–1112.

Valent P, Klion AD, Horny HP, et al.(2012) Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 130(3):607–612, e9.

Van Den Hoogenband, H.M. (1982) Skin lesions as the first manifestation of the hypereosinophilic syndrome. *Clinical and Experimental Dermatology*, 7, 267–271.

Vardiman JW, Bennett JM, Bain BJ, Brunning RD, Thiele J. (20018)Atypical chronic myeloid leukaemia,*BCR-ABL1* negative. In: Swerdlow S, Harris NL, Stein H, Jaffe ES, Theile J, Vardiman JW, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 80-81.

Vigna, E., Lucia, E., Gentile, M., Mazzone, C., Bisconte, M.G., Gentile, C., Armentano, A., Ottaviani, E., Rondoni, M., Martinelli, G. & Morabito, F. (2008) PDGFRalpha/FIP1L1-positive chronic eosinophilic leukemia presenting with retro-orbital localization: efficacy of imatinib treatment. *Cancer Chemotherapy and Pharmacology*, 61, 713–716

Zoi K, Cross NCP (2015)Molecular pathogenesis of atypical CML, CMML and MDS/MPN-unclassifiable.Int J Hematol.101(3):229-242

Wang SA, Hasserjian RP, Fox PS, et al (2014)Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. Blood. 123(17):2645-2651