Bölüm
2

KLL'DE OLUŞAN GENETİK DEĞİŞİKLİKLER

Sedanur KARAMAN GÜLSARAN[1]

GİRİŞ

Kronik lenfosittik lösemi (KLL) yaşlı nüfusun en yaygın erişkin lösemi hastalığıdır. KLL oldukça heterojen bir seyir göstermektedir. Bazı hastalar için takip yeterli iken, bazılarında hastalık hızlı seyir göstermektedir[1]. Bu klinik heterojenite, altta yatan moleküler ve hücresel çeşitliliğe bağlıdır[2]. KLL genetiğinin daha iyi anlaşılması, bu hastalığın prognozunu belirlemede ve tedavide önemlidir.

Floresan insitu hibridizasyon (FISH) yöntemi kullanılarak KLL hastalarının %80'ninde sitogenetik anormallikler saptanabilmektedir[3, 4]. Konvansiyonel karyotip analizinde ise hastaların ancak %20-50'sinde kromozomal anomaliler saptanmaktadır; bu nedenle FISH yöntemi konvansiyonel sitogenetik yönteme göre daha sensitiftir[5]. KLL hastalarında FISH yöntemi kullanarak yapılan çalışmalarda del 13q14 en sık görülen genetik anormallik olup tüm hastaların yaklaşık %50'sinde bulunmaktadır. Ayrıca, hastaların yaklaşık %15-20'sinde trizomi 12 ve %10-15'inde 11q22.3 genetik mutasyonu görülmektedir. Tespit edilen diğer anormallikler ise del 6q21 ve del 17p13.1 olup, bu anormallikler hastalık sonuçları üzerinde farklı prognostik etki yaratmaktadırlar[6]. Kompleks genomik değişiklik daha önce tedavi edilmemiş hastaların %15-30'unda saptanmaktadır ve hızlı hastalık progresyonu, Richter transformasyonu ile ilişkili olup bu hastalarda prognoz daha kötüdür[7, 8].

Yapılan sitogenetik incelemeler ve FISH yöntemi ile hastalığın erken dönemlerinde tekrarlayan aberran mutasyonlar sıklıkla gözlenmezken, hastalığın seyri sırasında mutasyonların ortaya çıktığı görülmüştür[9]. Bu nedenle tedavi değişikliği planlanırken tekrar FISH analizlerinin yapılması önerilmektedir[10].

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BIRC3

Baculoviral IAP Repeat Containing 3 (BIRC3) geni, alternatif NF-kB sinyal yolunun negatif regülatörüdür. Olguların %5-8'inden daha azında görülen BIRC3 gen mutasyonu alternatif NF-kB yolunun aktivasyonuna yol açar[63]. ATM ve BIRC3 genleri kromozom 11q bölgesinde bulunur. Tanı anında %4 BIRC3 mutasyonu saptanır iken kemoterapiye dirençli KLL'de %24'e çıkabilmektedir.

KOMPLEKS KARYOTİP VE TRANSLOKASYON

Kompleks karyotip, konvansiyonel kromozom bantlama yöntemi ile 3 veya daha fazla yapısal kromozomal anormallik varlığı olmasıdır. KLL'de kötü prognoz ile seyretmektedir. Kompleks karyotipe sahip olan hastalar normal karyotipli hastalara göre prognozu daha kötü seyretmektedir.

Translokasyonlar, KLL'de anlamlı bir alt küme oluşturmaz ve kompleks karyotipin veya trizomi 12 veya del13 gibi sitogenetik anormalliklerin bir parçası olma eğilimindedir[78, 79]. Çok nadir görülmekle birlikte interfaz FİSH ile yapılan küçük çalışmalarda KLL hastalarında %0-2 oranında t(14;18) bildirilmiştir[80-82]. Konvansiyonel sitogenetik yöntemlerle yapılan çalışmalarda Sen ve arkadaşları[83] 2215 KLL hastasının 2'sinde; Juliusson ve arkadaşları[84] ise 640 KLL hastasının 3'ünde t(14;18) tespit etmiştir. KLL'deki t(14;18) moleküler yöntemlerle çalışılmış ve farklı BCL-2 değerlerine sahip olduğu, folliküler B hücreli lenfomadan farklı olduğu gösterilmiştir.

SONUÇ

KLL heterojen seyir gösteren bir hastalık olup, hastalığın tanı anından takip eden süreçte yeni genetik anomaliler, mutasyonlar gelişebilmektedir. Tanı anında genomik olarak risk değerlendirmesi, hasta yönetimi için yararlı olmaktadır[85]. Hedefe yönelik tedavilerin, konvansiyonel tedavilerin önüne geçtiği dönemde, genetik bilgi hastalığın tanısında ve tedavisini planlamak için klinisyenlere yol gösterici olmaktadır.

Anahtar Kelimeler: KLL, genetik

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