

Bölüm 11

KRONİK LENFOSİTİK LÖSEMİ TEDAVİSİNDE BCL-2 İNHİBİTÖRLERİNİN KULLANIMI

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GİRİŞ

Kronik lenfositik lösemi (KLL) erişkinde en sık görülen lösemi olup Amerika'da her yıl yaklaşık 20,000 yeni KLL hastasına tanı koyulmaktadır¹. Hastalığın patogenezinde intrinsek veya ekstrinsek apoptoz sinyallerinin bozulması sonucu morfolojik olarak matur görünümlü B hücrelerinin kontrolsüz klonal artışı rol alır². İntrinsek apoptoz BCL-2 aile proteinleri tarafından kontrol edilmektedir. KLL ve bazı diğer hematolojik malignitelerde BCL-2 protein artışı ve bunun sonucunda pro-apoptotik proteinlerin sekestrasyonu sonrası malign klonun apoptozdan korunduğu ve kemoterapi direnci oluşturduğu gösterilmiştir^{3,4}. Hematolojik malignitelerde BCL-2 protein ailesini hedefleyen ilaçlar tedavide yeni bir çığır açmış olup bu bölümde BCL-2 inhibitörlerinin KLL tedavisindeki yeri anlatılacaktır.

APOPTOZ VE BCL-2 AİLE PROTEİNLERİ

Apoptoz doku homeostazisi için kritik role sahip programlanmış hücre ölümüdür. Ekstrinsek(death receptor) ve intrinsek(mitokondriyal) yolak aracılı apoptoz olarak ikiye ayrılmaktadır. DNA hasarı veya büyüme faktörlerinin azalması sonrası intrinsek yolak aktive olur. Mitokondriden apoptotik protein olan sitokrom *c* salınması ve kaspas aktivasyonu sonucu programlı hücre ölümü gerçekleşir. Bu süreçte "geri dönüşüz" evre mitokondriyal dış membran permeabilitesinin (MOMP) bozulması olup bu süreç B cell lymphoma-2(BCL-2) aile proteinleri tarafından kontrol edilir⁵.

BCL-2 geni ilk kez 1980'lerde t(14;18) translokasyonu sonucu açığa çıkan gen ürünü olarak folliküler lenfomada tanımlanmıştır⁶ ve ayrıca tümör hücresi sağ kalımında üzerinde çalışılmış ilk onkogendir⁷. Bu dönem sonrasında günümüze

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olmasıdır. Bu durum KLL tedavisinde yaşlı, komorbiditesi olan, TP53 aberasyonu olan ve daha önce BCRI tedavisi almış ve yanıtız/yanıt kaybı olan hastalarda venetoklaks kullanımının tedavideki ihtiyacı karşılayacağını düşündürmektedir. Venetoklaks'ın monoklonal anti-CD20 ile kombinasyonu ilacın sabit süre kullanımına ve daha derin yanıtlar elde edilmesine olanak sağlamıştır. Monoterapi ve kombinasyon çalışmalarındaki yan etkiler yönetilebilir olup yapılan doz artış protokolü ile TLS önlenebilmektedir. BCRI ile kombine çalışmaların umut vadeden ilk sonuçları açıklanmıştır. Günümüzde venetoklaks tedavisi ile en iyi yanıt elde edebilmek ve en az yan etkiyi oluşturmak amaçlı kombinasyon çalışmaları hala devam etmektedir.

Anahtar Kelimeler: KLL, BCL-2 proteini, Venetoklaks

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