Bölüm 9

KÜÇÜK HÜCRELİ DIŞI AKCİĞER KANSERİNDE PREDİKTİF VE PROGNOSTİK BİYOBELİRTEÇLER

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GİRİŞ

Akciğer kanseri, Globocan 2012 verilerine göre dünya genelinde en sık tanı alan kanser ve kansere bağlı ölümlerin başlıca nedenidir. 2012 yılında, dünya çapında yılda tahmini 1,8 milyon yeni olgu ve 1,59 milyon ölüm kaydedilmiştir.

Akciğer Kanseri Mutasyon Konsorsiyumunun (Lung Cancer Mutation Consortium-LCMC) katılımcı kurumları, klinisyenlerin hedefli tedavileri seçmesine ve klinik araştırmalara hasta almasına yardımcı olmak için 10 geni onkojenik sürücü mutasyonlar açısından analiz etmiştir (1). Moleküler analize göre küçük hücreli dışı akciğer adenokarsinomunda en yaygın üç onkojenik sürücü mutasyon; KRAS mutasyonları, EGFR mutasyonları, ALK rearranjmanları proliferasyon ve apoptoz dahil hücre fonksiyonlarını düzenleyen sinyal iletim yolaklarında rol oynar (2). Akciğer kanserinde son zamanlarda hem patogenezini anlama hem de tedavi yaklaşımlarını belirlemede büyük gelişmeler yaşanmıştır. Bu gelişmelerden sürücü mutasyonlar/moleküler değişiklikler kanserin başlangıcı ve gelişiminden sorumludurlar.

Prediktif biyobelirteç tedavinin etkinliğini öngörür, çünkü biyobelirteç ve tedavi sonuçları arasında bir ilişki vardır. Prognostik biyobelirteç tümörün doğal agresifliğini gösterir. Çünkü verilen tedaviden bağımsız olarak hastanın sağkalımı ile ilgili bir göstergedir. Burada küçük hücreli dışı akciğer kanserinde (KHDAK) en sık görülen biyobelirteçlerden bahsedeceğiz.

EGFR MUTASYONU

Epidermal growth factor receptor (EGFR) hücre membran reseptörüdür ve kromozom 7p11.2' de lokalizedir (3). Avian erythroblastic leukemia viral (v-erb-b) oncogene (ERBB1) olarak da bilinir (3). İnsanda yetersiz ERBB sinyali bazı nörodejeneratif hastalıklarla birlikte görülürken aşırı ERBB sinyali solid tümör gelişimi ile ilişkili bulunmuştur. (3). En sık mutasyonlar tirozin kinaz doma-

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mektedir (76). Metastatik nonsquamöz KHDAK'de EGFR ve ALK negatif olan ya da bilinmeyen hastalarda PD-L1 durumuna bakılmaksızın 1. basamakta kombinasyon olarak pembrolizumab/(ya da atezolizumab/ bevacizumab)/ kemoterapi NCCN 2019 3.versiyonda kanıt 1 düzeyinde önerilmektedir (76,77). Squamöz KHDAK'de Pembrolizumab/karboplatin/paklitaksel (ya da nab paklitaksel) PD-L1 düzeyine bakılmaksızın NCCN 2019 3.versiyonda kanıt 1 düzeyinde önerilmektedir (78). EGFR mutasyonu olan ve ALK rearranjmanı olan hastalarda PD-L1 ekspresyon düzeyinden bağımsız olarak anti PD1 ve PD-L1 ile monoterapi 2. basamakta daha az efektiftir (79,80,81). Yine EGFR mutant hastalarda PD-L1 ekspresyonu %50 den daha fazla olanlarda dahi 1. basamakta pembrolizumab efektif değildir (82).

Her ne kadar PD-L1 ekspresyonu optimal bir biyobelirteç olmasa da günümüzde anti PD-1 ve anti PD-L1 tedavi için uygun hasta seçiminde mevcut biyobelirteçler arasında en iyisidir. PD-L1 ekspresyonu sürekli değişken ve dinamiktir, bu nedenle pozitif bir sonuç için eşik değer belirtmek doğru olmayabilir. Yüzde 50'nin hemen altı ve üstü PD-L1 ekspresyonu olanlarda benzer sonuçlar görülebilmektedir (83). Pozitif test sonucu tanımı da hangi biyobelirteç test yöntemi kullanıldığına göre değişmektedir. Bu bağlamda tümör mutasyon yükünü (TMB) belirleyen çeşitli ölçümler araştırılmaktadır (84). TMB'nin nasıl ölçülebileceğine dair konsensus geliştirmek için uluslararası bir çaba sarf edilmektedir (85, 86, 87). Ayrıca tümör inflamasyonunun değerlendirilmesi için de çeşitli yöntemler geliştirilmektedir fakat bunların rutinimize girebilmesi için daha fazla çalışmaya ihtiyaç duyulmaktadır (29).

SONUÇ

Son yıllarda geliştirilen moleküler testler sayesinde KHDAK'nin hem patogenezi, hem prognozu hem de tedavi hedeflerinin belirlenmesinde ilerlemeler kaydedilmiştir. Aynı zamanda bu testler tedavi direnç mekanizmalarının anlaşılmasında ve çözümünde de rol almaktadır. Şüphe yok ki, geliştirilen moleküler test yöntemleri ile gelecekte KHDAK'li birçok hastanın tümör genotipleme ile belirlenmiş spesifik tedavisi olacağı düşünülmektedir.

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