Bölüm
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AKCİĞER KANSERİ'NDE KULLANILAN TİROZİN KİNAZ İNHİBİTÖRLERİNE KARŞI GELİŞEN DİRENÇ MEKANİZMALARI VE TEDAVİ YAKLAŞIMLARI

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GİRİŞ

Tirozin kinaz inhibitörleri (TKI), küçük hücreli dışı akciğer kanseri (KHDAK) tedavisinde epitelyal membranda gelişen sensitize edici mutasyonların varlığında, dikkate değer bir sağkalım avantajı sağlamakla birlikte, tedavi sonrasında gelişen kazanılmış mutasyonlar, beklenen etkinlikte hayal kırıklıkları yaratmış, onkoloji kongrelerinde geniş bir yer bulan, yeni kazanılmış mutasyonların tespiti ve hedeflenmesine yönelik ilaç geliştirilmesi adına, yeni ve dinamik bir alan gelişmesine yol açmıştır.

TKI'ın hedeflediği ve klinik pratikte sıklıkla kullanılan sürücü mutasyonlar; epitelyal büyüme faktörü reseptör (EGFR) genini hedefleyen mutasyonlar ve anaplastik lenfoma kinaz (ALK) ve ROS protoonkogen 1 (ROS1) domainlerinde disregülasyona yol açan füzyon mutasyonlarıdır.

EGFR'nü hedef alarak geliştirilen anti-EGFR ajanları, yolculuğuna mutasyondan bağımsız olarak tüm adenokanserli popülasyonu hedefleyerek başlamış, ancak etkinliğinin daha çok kadın, sigara içmeyen ve eski sınıflamaya göre bronkoalveolar adenokasinom patolojik alt tipinde daha fazla olduğu gösterilmişti ki, aslında bu etkinliğin bu alt gruplarda EGFR mutasyon oranlarının görece daha yüksek olması ile ilişkili olduğu sonradan anlaşıldı. Sonrasında anti-EGFR ajanlara yanıtı predikte eden belirli mutasyonların tespiti ile spesifik gruplar belirlenerek, bu gruplarda 1. jenerasyon anti-EGFR ajanlar olan erlotinib ve sonrasında gefitinib ile kemoterapiye üstünlük gösterilmesine karşın, genel sağkalıma yansımayan etkinlik, daha potent ajanların arayışını beraberinde getirdi. Hedef mutasyona geri dönüşsüz olarak kovalan bağlanan ikinci jenerasyon ajanlar olan

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hasta gruplarında, ALK ve ROS1 positif hastalarda etkinliği değerlendirilmiş, SSS metastazı olan hastaları da içeren çalışmasında, %47 (%39.9-%54.2)' ye varan objektif yanıt oranlarına ulaşılmıştır (47). Bu nedenle ALK ve ROS1 TKI tedavisi sonrası progresyon gelişen hasta popülasyonunda sıralı tedavide yerini almıştır.

Bu tedaviler dışında immünoterapi ile ALK TKI kombinasyonu ya da sıralı tedavisi 2018 ASCO' da sunuldu ancak çok toksik olarak değerlendirilmiştir (Abstract 9008).

SONUÇLAR

ALK TKI tedavilerinde tedavi direncini yenmek adına daha potent ajanlar olan alektinib ve brigatinib' in kullanımı önerilmektedir. Daha potent ajanlar sonrası daha yüksek oranda gelişen gelişen ALK direnç mutasyonu varlığı, 3.jenerasyon ALK TKI olan lorlatinib' e yanıtı predikte etmektedir ve progresyon sonrası doku biyopsisi tedavi için prediktiktif bilgiler sunmaktadır.

Anahtar Kelimeler: Tirozin kinaz inhibitörleri, kazanılmış mutasyonlar, küçük hücreli dışı akciğer kanseri, tedavi

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