BÖLÜM 21

HİPOMETİLE EDİCİ AJANLAR

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GİRİŞ

Azasitidin (5-azasitidin, AZA) ve desitabin (5-aza-2′-deositidin, DAC), sitidinin düşük ancak klinik olarak anlamlı konsantrasyonlarda DNA metiltransferazları (DNMT'ler) inhibe ederek etki gösteren geçici ve değişken DNA hipometilasyonunu sağlayan iki farklı analoğudur.

Hipometile edici ajanlar (HMA'lar), miyelodisplastik sendrom (MDS), kronik miyelomonositik lösemi (CMML) ve akut miyeloid lösemi (AML)'de aktif bir şekilde standart tedavilerde kullanılmaktadır. Ancak, hasta yanıtları heterojenite göstermektedir.

Bu bölümde, HMA'lar ve miyeloid malignitelerde HMA'ların kullanımına ilişkin güncel durumdan bahsedilecektir. Ayrıca, HMA'ların gelişen uygulamalarına, şu anda geliştirilmekte olan yeni HMA'ların etkinliğine ve HMA tabanlı kombinasyonların faydasına ilişkin bir genel bakıştan bahsedilecektir.

HMA'LARIN ETKİ MEKANİZMASI

HMA'ların metabolizması son zamanlarda ayrıntılı olarak gözden geçirilmiştir (1). Şekil 1'de de etki mekanizması özetlendiği üzere HMA'lar absorpsiyondan sonra, spontan hidroliz ve sitidin deaminaz (CDA) tarafından deaminasyona uğraması nedeniyle plazma konsantrasyonları kararsızdır, bu da ajanların göreceli kısa plazma yarı ömürlerini açıklar (2). Nükleosit taşıyıcılara bağlı olan hücresel alımlarını takiben, hücre içi kinazlar tarafından art arda fosforile edilirler. DAC'ın (5-aza-dCTP) aktif tri-fosforile metaboliti, hücre döngüsü sırasında doğrudan DNA'ya dahil edilir. DNA'ya dahil edilen 5-aza-dCTP, DNMT1'i bağlar ve bozul-

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kemoterapi için uygun olmayan, tedavi edilmemiş yaşlı AML'de AZA ile ilişkili olarak PEV'i değerlendiren bir faz 1b çalışması , %50'lik bir genel yanıt oranı ile kabul edilebilir bir güvenlik profili bildirmiştir. Randomize faz 3 klinik deneyi PANTHER şu anda tedavi edilmemiş MDS, CMML ve düşük blast sayısı AML'de (NCT03268954) AZA + PEV ile AZA'yı tek başına karşılaştırmaktadır (4).

SONUÇ

HMA'lar on yıldan fazla bir süredir miyeloid malignitelerde kullanılmaktadır. Tek hücreli epigenomikteki ilerleme, HMA'ların etki mekanizmalarını anlamamıza yardımcı olmaktadır. Bu durum sonunda hangi hastaların HMA tedavisinden fayda göreceğini tahmin etmek için sağlam biyobelirteçleri belirlememize yardımcı olacaktır.

HMA endikasyonlarının spektrumu, özellikle bakım veya önleyici tedavi olarak şu anda genişlemektedir. İkinci nesil HMA'lar miyeloid malignitelerde halen değerlendirilmektedir. İlk sonuçlar, AZA veya DAC'den üstün olamayabileceklerini göstermektedir, ancak oral formülasyonun en azından hasta uyumu ve doz adaptasyonunu optimize edeceği düşünülmektedir. Kombinasyon tedavileri tek ajanlardan üstün olabilir. Bu durumun deneysel olarak mı yoksa rasyonel bir klinik öncesi tarama yoluyla mı aranmaları gerektiği halen belirsizliğini koruyor. Bununla birlikte, HMA'lar önümüzdeki on yılda miyeloid neoplazmalara karşı silahlanmanın önemli bir parçası olarak kalma potansiyeline sahiptir.

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