BÖLÜM 10

ALKİLLEYİCİ AJANLARIN ETKİ MEKANIZMALARI VE SINIFLANDIRILMASI

Murat ESER[1]

ALKİLE EDİCİ MADDELERİN TARİHÇESİ

Bir nitrojen ve hardal alkilleyici ajan, önemli klinik antitürnör aktivite gösteren ilk hormonal olmayan kimyasaldır. Antitümör ajanlar olarak nitrojen mustardların klinik değerlendirmesi, I. Dünya Savaşı'nda silah olarak kullanılan kükürt hardal gazının gözlemlenen klinik etkilerinden evrimleşmiştir. Bu gaz, cilt ve mukoza zarları, özellikle gözler ve solunum yolu üzerindeki vezikan etkisi nedeniyle kullanılmıştır (1). Bununla birlikte, bu ölümcül etkiye ek olarak, kurbanlarda ve deney hayvanlarında hematopoietik ve lenfoid sistemlerin depresyonu gözlemlendi(2). Bu gözlemler, daha az uçucu nitrojen mustardları kullanan daha ileri çalışmalara yol açtı. 1946'da yayınlanan çalışmalar, tümörlerin, özellikle lenfomaların(3-5) gerilediğini gösterdi ve bileşik nitrojen mustardın (mekloretamin, mustargen) klinik uygulamaya girmesine yol açtı. Daha sonra, daha az toksik ve klinik olarak daha etkili nitrojen türevleri ve diğer alkalileştirici ajan türleri geliştirilmiştir.

ALKİLE EDİCİ AJANLARIN KİMYA VE SİTOTOKSİSİTESİ

Alkilleyici ajanlar, hücrelerdeki birçok elektronca zengin atomu kovalent bağlar oluşturmak üzere reaksiyona sokar (veya "alkile eder"). Antitümör aktiviteleri açısından en önemli reaksiyonlar DNA bazları ile olan reaksiyonlardır. Bazı alkilleyici ajanlar monofonksiyoneldir ve sadece bir DNA dizisi ile reaksiyona girer. Diğerleri iki işlevlidir ve DNA çift sarmalının iki sarmalını kovalent olarak bağlayan bir "çapraz bağlantı" üretmek için DNA'nın iki sarmalının her biri üzerindeki bir atomla reaksiyona girer. Onarılmadığı takdirde, bu lezyon hücrenin etkili bir

[1] Uzm. Dr, Erciyes Üniversitesi Medikal Onkoloji Bölümü, eserkayseri_83@hotmail.com

Bu ajan, 2000 mg/m2'lik bir dozda kemik iliği transplantasyonunda kullanılan tek bir ajandır (153). Bu dozda, dakarbazinin maksimum plazma konsantrasyonu 800 uM'dir(153).Temozolamid genellikle 5 gün süreyle 150 ila 250 mg/m2/gün oral olarak verilir. Reid ve diğerleri (154) bu temozolamid dozlarının ayarlanmasından sonra 0,5 ila 5 uM'lik MTIC pik konsantrasyonlarını ölçtüler(154). Baker ve diğerleri(155), 14C etiketli temozolomidin farmakokinetiğini inceledi ve temozolomidin pik konsantrasyonlarını yaklaşık 30 uM ve tepe kansantrasyonlarını yaklaşık olarak 1 uM MTIC buldu.

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