BÖLÜM 23

POLİ (ADP-RİBOZ) POLİMERAZ İNHİBİTÖRLERİ

Ömer ACAR[1]

GİRİŞ

DNA hasarı normal hücre döngüsü sırasında sık görülen bir olaydır. Hücre metabolizma sırasında spontan veya çevresel nedenler nedeniyle DNA hasarı meydana gelebilir (1). Doğru şekilde onarılmazsa tek iplikçikli DNA kırıkları veya çift iplikçikli DNA kırıklarına neden olarak genom bütünlüğünün bozulmasına ve sonunda instabil hale gelerek hücre ölümüne neden olur (2). Normal hücresel metabolizmada ve DNA hasarı geliştikten sonra onarımda çok sayıda tamir mekanizması vardır (Şekil 1). Bunlar baz eksizyon tamiri (BER), nükleotid eksizyon tamiri (NER), mismatch (yanlış eşleşme) eksizyon tamiri (MMR), translezyonel sentez, homolog rekombinasyon eksikliği (HR) ve homolog olmayan tamir (NHEJ) yoluyla yapılır (3-4). HR ve NHEJ çift sarmal kırıklarını onarmada görevlidir. HR özellikle hücre döngüsünün G2-S safhasında aktif olup yüksek doğrulukta tamir mekanızmasından sorumludur (5-6). NHEJ daha hızlı tamir mekanızmasına sahiptir fakat hataya açıktır (7-8). Bir hücrede homolog rekombinasyon eksikliği (HRD) oluşursa tamir mekanizması NHEJ yoluna kayar ve bu da genom stabilitesine zarar vererek kanser gelişmesine neden olabilir (9). İlk çalışılan HR proteinleri BRCA1 ve BRCA2 meme ve over kanser gelişimine neden olur (10-14). DNA tamiri yaklaşık 150 gen içeren komplex bir olaydır (15). Tek sarmal DNA kırıkları tamiri ve homolog rekombinasyon tamiri eş zamanlı kusurlu olduğunda hücre yaşayamaz buna sentetik letalite teorisi denmektedir (16). Çalışmalarda BRCA mutant hastalarda PARP inhibitörleri etkili bulunmuştur (17).

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PARP İNHİBİTÖRLERİN YAN ETKİLERİ

PARP inhibitörlerinin monoterapi veya kemoterapi ile kombine kullanımları anemi, trombositopeni, nötropeni gibi ciddi hematolojik yan etkilere neden olabilir (54). Olaparib kullanırken ciddi nötropeni daha sık görülür. Veliparib kullanımında trombositopeni ve nötropeni gelişimi yaygındır (55). Rucaparip kullanan hastalarda yorgunluk, asteni, bulantı, kusma, anoreksiya, kilo kaybı, ishal, kabızlık, trombositopeni, kreatin artışı, karaciğer transaminaz artışı görülmüştür (56-57). Akut myeloid lösemi (AML) ve miyelodisplastik sendrom (MDS) gelişimi nadiren görülür (58). Master, Mansour ve arkadaşlarının yaptığı meta analizde olaparib kullanan hastalarda daha sık olmakla birlikte olaparip, niraparib ve rucaparib kullanan hastalarda AML ve MDS görülme oranı %2,9 olarak bulunmuştur (59).

SONUÇ

PARP inhibitörleri PARP enziminin katalitik alanına bağlanarak replikasyon çatalının durmasına neden olur. Genom bütünlüğü bozularak sonunda kanserli hücrenin ölmesine neden olurlar. Özellikle BRCA mutasyonu veya homolog rekombinasyon eksikliği bulunan hastalarda progresyonsuz sağ kalım ve genel sağ kalım katkısı vermişlerdir. FDA onayı alan PARP inhibitörleri olaparip, niraparip, talazoparip ve rucaparip olup veliparip onay alma aşamasındadır. Grade 3 yan etki en çok yorgunluk, anemi ve trombositopenidir.

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