Bölüm
9

KRONİK LENFOSİTİK LÖSEMİ'DE BRUTON TİROZİN KİNAZ İNHİBİTÖRLERİ

Sude Hatun AKTİMUR[1]

İBRUTİNİB

Malign B hücreli neoplastik hastalıkların gelişimi açısından B hücre reseptör (BCR) patolojik ekspresyonunun önemi bilinmektedir (1). Normal B lenfositler, BCR'ye eksternal bir antijenin bağlanması ile tetiklenen sinyalleri BCR'den alırken, BCR üzerinden gelen sinyaller kronik lenfositik lösemi (KLL) hücrelerinin büyümesini sağlamakta ve hastalığın patogenezinde etkin rol oynamaktadır. Bruton tirozin kinaz (BTK), neoplastik sinyalleri BCR ve doku reseptörlerinden alan bir sitoplazmik tirozin kinazdır (2). BTK inhibitörü olan ibrutinib, BTK'yı selektif, irreversibl inhibe eden, hedefe yönelik bir ajandır. Özellikle KLL, mantle hücreli lenfoma (MHL) ve Waldenstrom makroglobulinemisi (WM) gibi B hücre malignitelerinde etkin bir tedavi seçeneğidir. (3, 4). İbrutinibin özellikle relaps-refrakter KLL hastalarında kalıcı hastalık kontrolü, artmış PFS ve OS sağladığı gösterilmiştir (5). İbrutinib ile tedavinin erken döneminde, dokuda yeralan malign B hücreleri, periferik kana doğru ilerler ve lenfositozda dalgalanmayla beraber belirgin yükselme de görülebilir. Büyümüş lenf nodları hızlıca küçülür. İbrutinib, soluble ve selüler moleküler elementleri etkileyerek KLL'deki tümör mikroçevresinin kompozisyonunu ciddi şekilde değiştirir ve myelosüpresyona sebep olmaz (4) Sürekli uygulanan ibrutinib tedavisi ile haftalar/aylar içinde lenfosit sayısı normalize edilir ve KLL hastalarının büyük çoğunluğunda remisyon gözlenir.(6). İbrutinib klinikte kullanılan, onay almış ve en fazla klinik veriye sahip ilk BTK inhibitörüdür. BTK proteinini selektif ve irreversibl olarak inhibe etmesi için tasarlanmıştır ve BCR den sinyal transdüksiyonunu inhibe ederek B hücrelerinin aktivasyonunu bloke etmektedir.

1 Samsun Eğitim ve Araştırma Hastanesi, İç hastalıkları ve Hematoloji Uzmanı

- Folliküler B hücreli NHL: En az 2 sistemik tedavi almış relaps folliküler B hücreli NHL tedavisinde
- Küçük lenfositik lösemi: En az 2 sistemik tedavi almış relaps küçük lenfosittik lösemi (SLL) tedavisinde

FARMAKOKİNETİĞİ

Önerilen doz günde 2 defa 150 mg oral idelalisib uygulanmasıdır. Oral uygulamadan 2-4 saat sonra pik plazma konsantrasyonuna ulaşır. Primer olarak karaciğerde aldehit oksidaz ve CYP3A ile metabolize edilir. Eliminasyon yarı ömrü 8.2 saattir. Büyük kısmı feçes (%78), daha azı ise idrar (%14) ile atılır.

Yan etki profili:

Monoterapi ile >%10 rapor edilen:

- SSS: Halsizlik (%30), insomnia (%12), başağrısı (%11)
- Dermatolojik: Rash (%21), gece terlemeleri (%12)
- GIS: Diare (%47), bulanto (%29), karın ağrısı (%26), iştahsızlık (%16), kusma (%15)
- Hematolojik ve onkolojik: Hb düşüklüğü (%28, evre 3: %2), PLT düşüklüğü (%26, evre 3: %3, evre 4: %3), nötropeni (%25, evre ¾)
- Hepatik: ALT yüksekliği (%50), AST yüksekliği (%41), ciddi hepatotoksisite (%18)
- Enfeksiyon: Sepsis ve febril nötropeni gibi ciddi enfeksiyonlar (%21)
- Respiratuar: Öksürük (%29), pnömoni (%15-25), dispne (%17), ÜSYE (%12)
- Diğer: Ateş (%28)

Monoterapi ile %1 - 10 rapor edilen:

- KVS: periferik ödem (%10)
- Respiratuar: Pnömonitis (%4)

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