YENİ İLAÇLARIN HEDEFİ OLARAK ONKOGENLER

24. BÖLÜM

Çağlar ÜNAL[1]

GİRİŞ

Protoonkogenler hücrelerin büyüme ve farklılaşmasında rol alan büyüme faktörleri ile bu büyüme faktörlerinin sinyal iletiminde yer alan proteinleri (reseptörler, sitoplazmik proteinler ve çekirdekte yer alan transkripsiyon faktörleri) kodlayan genlerdir. Protoonkogenler; insersiyon, nokta mutasyonu, kromozomal translokasyon, gen amplifikasyonu ve virüsler aracılığıyla gelişebilen transdüksiyon aktivasyonu yolu ile onkogenlere dönüşürler ve bu onkogenler tümör gelişimine neden olurlar .(1)

N-myc, bcl-2, RET, K-ras, N-ras, Akt-1, Akt-2, FOS, JUN, MET, C-myc, L-myc, H-ras, c-ERBB2, NTRK, WNT-1, BRAF, KİT bilinen onkogenlerden bazılarıdır..

AKT-1 ve AKT-2 amplifikasyonu mide kanserinde,(2) BRAF mutasyonları en sık tiroid kanseri, melanoma, kolorektal ve küçük hücre dışı akciğer kanserinde (KHDAK) görülmektedir.(3) CTNNB1 mutasyonu ise kolon kanseri, melanom, serviks ve endometrium kanserinde saptanmıştır. (4) İnsan epidermal büyüme faktörü (HER) ailesinin dört üyesi EGFR/HER1/ErbB1/, HER2/ErbB2, HER3/ErbB3 ve HER4/ErbB4 olarak belirtilmektedir.(5) Her-2 geni, transmembran bir tirozin kinaz reseptörünü kodlayan onkogendir. Erb-B2 onkogeni nokta amplifikasyonu başta meme kanseri olmak üzere mide, özofagus, akciğer, endometrium, kolon, pankreas ve mesane kanserinde görülmektedir.(6)

Meme kanseri tanılı hastaların %15-20'sinde Her-2 gen amplifikasyonu (7), metastatik mide kanseri tanılı hastaların ise yaklaşık %22'sinde Her-2 amplifikasyonu ya da aşırı ekspresyonu izlenmektedir.(8) Lenf nodu metastazı ve kötü prognoz ile seyreden hastalarda aşırı Her-2 expresyonu görüldüğü tespit edilmiştir.(9) MET nokta mutasyonu herediter ve sporadik papiller renal kanseri (10) ve mide kanserinde,(11) ayrıca baş ve boyun tümörlerinin lenf nodu metastazında saptanırken(12), MET amplifikasyonu ise özofagus, mide kanseri, (13) ve KHDAK'de saptanmıştır.

C-MYC ekspresyonları Burkit lenfoma, melanom, kolorektal, meme ve prostat kanserinde, N- MYC nöroblastoma, L-MYC ise küçük hücreli akciğer kanserinde görülmüştür.(14)

K-ras mutasyonu tüm tümörlerin %22'sinde, N-ras ise %8'inde, H-ras %3'ünde saptanmıştır. (15) K-ras mutasyonu sıklıkla kolon, pankreas, safra yolları, ince barsak, akciğer ve endometrium tümörlerinde, N-ras hematopoetik ve lenfoid maligniteler, cilt, tiroid ve over kanserinde tespit edilmektedir. H-ras mutasyonu ise tükürük bezi, üriner sistem, prostat ve üst gastrointestinal tümörlerinde görülmektedir.(16)

İlk olarak monoklonal antikorlardan rituximab ve trastuzumab, tirozin kinaz inhibitörlerinden (TKİ) ise imatinib'in keşfedilmesiyle birlikte onkogenleri hedef alan tedaviler açısından günümüze kadar çok yol kat edilmiştir(17-19) ve hala hedefe yönelik tedaviler açısından birçok klinik çalışma devam etmektedir.

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Encorafenib: Bir protoonkogen olan ve B-raf proteinini kodlayan B-RAF genini inhibe etmektedir. Bu protein hücre bölünmesini, diferansiyasyonu sağlayan MAP kinaz / ERK sinyal yolağının düzenlenmesinde rol oynamaktadır. BRAF V600E mutasyonu tedavi altında progrese metastatik kolon kanseri tanılı hastalarda encorafenib + cetuximab ± binimetinib ile kombinasyon tedavisinde ve metastatik yada unrezektabl melanoma tanılı hastalarda encorafenib + binimetinib ile kombinasyon tedavisi kullanılmaktadır.[101,102]

3. jenerasyon B-RAF inhibitörleri (pan-RAF inhibitörleri) olan LY3009120, TAK-580, CCT196969, CCT241161 and BGB659 ile klinik çalışmalar bulunmaktadır.[103]

SONUÇ

Onkogenler üzerinde yapılan klinik çalışmalar sayesinde birçok hedefe yönelik tedavi seçenekleri bulunmuştur ve bulunmaya devam etmektedir. Her bir onkogene yönelik yapılan çalışmalar ışığında özellikle metastatik evre (histolojik tip farketmeksizin) kanser tedavisi açısından tüm dünya genelinde yoğun bir şekilde üzerinde durulmaktadır. Hedefe yönelik tedaviler immün kontrol noktası inhibitörlerinin de geliştirilmesiyle son 10-20 yıl içerisinde önemli bir yol kat etmiştir. İleriki zamanlarda her bir onkogene ve onun mutasyonuna spesifik ilaçların gelişeceği umulmaktadır**.**

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