BÖLÜM 19

KEMOTERAPİYE DİRENÇLİ MEME KANSERİ TEDAVİSİNDE YENİ UFUKLARA DOĞRU: UZUN KODLAMAYAN RNA'LAR

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Giriş

Küresel ölçekte kadınlarda en sık görülen kanser tipi olan meme kanseri, dünyada kansere bağlı ölüm nedenleri arasında akciğer kanserinden sonra ikinci sırada gelmektedir (1). Yalnızca 2018 yılında yaklaşık 2,1 milyon kadının meme kanseri tanısı aldığı ve yaklaşık 627.000 kadının meme kanserine bağlı olarak yaşamını yitirdiği tahmin edilmektedir (1,2). Meme kanserinin epidemiyolojik verilerinin Türkiye'de de buna paralel olduğu görülmektedir: 2018 yılında 22345 vaka ile akciğer kanserinin ardından en sık görülen kanserdir ve 5432 ölüm ile kansere bağlı ölüm nedenleri arasında 5'inci sıradadır (3).

Erken teşhis olanaklarının artmasının yanı sıra tedavideki gelişmelerin sonucu olarak meme kanserinde 5 yıllık sağ kalım süresinde çok belirgin bir artış gerçekleşmiştir. 2018 yılında hastaların büyük bir oranda (%62) henüz metastazların olmadığı başlangıç evresinde iken tanı aldığı ve tedavi ile 5 yıllık sağ kalım oranlarının yaklaşık %99'a ulaştığı hesaplanmaktadır (4). İnvaziv meme kanseri hastalarında ise 5 yıllık sağ kalım oranı %90 civarındadır (5). Bu yüz güldürücü sonuçlara rağmen meme kanseri insidansındaki artış önemli bir risk oluşturmaktadır: 2012 yılında dünya ölçeğinde yeni tanı alan meme kanseri hastası sayısı 1,7 milyon iken 2018 yılında bu sayının 2,1 milyona ulaştığı hesaplanmaktadır (1,6). Yeni tanı alan meme kanseri hasta sayısındaki artış yaklaşık %24'tür. Bu durum meme kanseri tedavisinin başarısını artıracak yaklaşımların önemini artırmaktadır.

Günümüzde meme kanseri tedavisinde kullanılan anti-HER2 (Human Epidermal growth factor Receptor 2) ilaçların yanısıra mTOR (mammalian target of rapamycin) inhibitörü everolimus ve CDK4/6 (Cyclin Dependent Kinase 4/6) inhibitörleri paklosiklib ve ribosiklib gibi yeni ilaçlar endokrin tedavi ile birlikte meme kanserinde

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Sonuç

Uzun kodlamayan RNA'ların ekspresyonlarının diğer birçok kanser türünde olduğu gibi meme kanserinde de farklılaştığı bilinmektedir (94). Doku dağılımlarının transkriptomun protein kodlayan üyelerine göre çok daha belirgin şekilde dokuya özgün olması uzun kodlamayan RNA'ların potansiyel olarak özgünlüğü çok yüksek tanısal belirteçler olarak kullanılabilmesine imkân sağlayacak gibi görünmektedir (11). Yakın zamanlarda uzun kodlamayan RNA RP11-445H22.4'ün meme kanseri hastalarında serum düzeylerinin belirgin ve anlamlı olarak yüksek olduğu gösterilmiştir. RP11-445H22.4'ün %92 duyarlık ve %74 özgünlüğü ile meme kanseri için duyarlı ve özgün bir biyobelirteç olabileceği bulunmuştur (95). Yakın zamanda yapılan başka birçok çalışmada kanser tanısı ve prognoz tahmini için tanısal belirteçler olarak etkinlikleri gösterilmiş olan uzun kodlanmayan RNA'ların (96-98) meme kanserinde ilaç direncinin gelişimindeki kilit önemdeki rolleri, yüksek düzeyde dokuya ve kanser tipine özgü ekspresyon paternleri ile birlikte düşünüldüğünde direnç gelişiminin öngörülmesini sağlayarak meme kanseri türüne özgü tedavi seçeneklerinin belirlenebilmesi için yüksek hassasiyete sahip biyomarkerler olarak kullanılabilecekleri görülmektedir.

Bunun yanı sıra, uzun kodlamayan RNA'ların meme kanserinde tedaviye direnç gelişimine hangi mekanizmalarla katkıda bulunduklarının açığa çıkarılması yeni tedavi yaklaşımlarının gerçekleştirilmesini olası kılacak ve üçlü negatif meme kanseri gibi birçok ilaca karşı dirençli kanser türlerinde tedavi başarısının artmasına ve sağ kalım oranlarının yükselmesine olanak verebilecektir.

Büyük bir hızla gelişen bir araştırma alanı olmasına rağmen uzun kodlamayan RNA'lar hakkında açığa kavuşmayı bekleyen pek çok nokta bulunmaktadır. Bununla birlikte gelecekte lncRNA bazlı tedavilerin geliştirilmesi olası görünmektedir. Onkojenik lncRNA'ların süprese edilmesi ya da süpresör lncRNA'ların indüklenmesi gibi yaklaşımlar tedavide ulaşılmayı bekleyen yeni bir ufuk çizgisi gibi durmaktadır.

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