Bölüm
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HER2/NEU POZİTİF MEME KANSERİNDE TEDAVİ SEÇENEKLERİ

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GİRİŞ

İnsan epidermal büyüme faktörü reseptörü (HER) ailesinin dört üyesi EGFR/HER1/ErbB1, HER2/ErbB2, HER3/ErbB3 ve HER4/ErbB4 olarak tanımlanmaktadır (Yarden and Sliwkowski 2001; Citri and Yarden 2006). HER2 geni, transmembran bir tirozinkinaz reseptörünü kodlayan onkogendir ve HER2-pozitif meme kanseri ve diğer bazı kanserlerde tümör gelişiminde önemli bir rol oynamaktadır (English, Roque, and Santin 2013). HER2 gen amplifikasyonu meme kanseri olgularının %15-20'sinde gözlenmektedir (Dawood et al. 2010),(Hilal and Romond 2016; Ponde et al. 2018). Aşırı HER2 ekspresyonu ile lenf nodu metastazı ve kötü prognoz arasında ilişki olduğu bilinmektedir (Lacroix et al. 1989),(Tan, Yao, and Yu 1997).

Son yıllarda trastuzumab, pertuzumab ve trastuzumab emtansin (T-DM1) gibi anti-HER2 tedavilerin kullanıma girmesiyle birlikte, HER2-pozitif, lokal ileri ya da metastatik meme kanserinin (MMK) prognozunda ciddi iyileşmeler sağlandığı rapor edilmektedir (Parakh et al. 2017). Bu tedaviler altında progresyon gelişen hastalarda kullanılmak üzere pek çok yeni tedavi ajanı ile ilgili çalışmalar da sürmektedir. Biz de MMK olgularında kullanılan ve araştırılmakta olan ajanları gözden geçirmeyi amaçladık.

1. SIRA TEDAVİLER

Trastuzumab

1998 yılında Amerika Birleşik Devletleri Gıda ve İlaç İdaresi (US FDA) tarafından onaylanmasının ardından trastuzumabın HER2-pozitif meme kanseri

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olup trastuzumab ile kombine olarak çoklu sıra tedavi almış HER2-pozitif MMK hastalarında faz Ib çalışmada değerlendirilmektedir (Keegan et al. 2018). Yine pan-sınıf I PI3K inhibitörü olan pilaralisibin (SAR245408), trastuzumab içeren rejimlerle progresyon gelişen HER2-pozitif MMK olgularında trastuzumab ya da paklitaksel-trastuzumab tedavilerine eklendiği faz I/II çalışmada paklitaksel kolunda klinik aktivite göstermektedir (Tolaney et al. 2015). Sınıf I PI3K inhibitörü olan MEN1611, faz Ib çalışmada trastuzumab ile kombine olarak, anti-HER2 tedavi uygulanmış, PIK3CA mutasyonu olan, HER2-pozitif MMK olgularında fulvestrant eklenen ve eklenmeyen kollar olarak araştırılmaktadır (B-PRE CISE-01 çalışması).

SONUÇ

HER2-pozitif MMK'nin tedavisi hızla değişemekte ve gelişmektedir. Günümüzde birinci sıra tedavide pertuzumab, trastuzumab ve dosetaksel kombinasyonu ile T-DM1 ciddi potansiyel taşımaktadır. Bu ajanlarla ciddi klinik yarar sağlanmış olsa da, neredeyse tüm hastalarda tedaviye direnç gelişmekte ve progresyon kaçınılmaz olmaktadır. Neyse ki HER2'ye karşı yeni ajanlar geliştirilmeye devam etmektedir. HER2 AİK, standart ikinci sıra tedavi olan T-DM1'in yerini alabilecek ya da T-DM1 sonrasında kendilerine yer bulabilecek seçenekler olarak görünmektedirler. Bu ajanların T-DM1'den en büyük farkının HER2'yi düşük düzeyde eksprese eden tümörlerde de etkinlik göstermeleri olarak belirtilmektedir. Neratinib ya da tucatinib gibi yeni geliştirilen TKI'lerin, toksisite önemli bir sorun olsa da, kapesitabin ile kombine olarak üçüncü sıra tedavide yer bulabilecekleri düşünülmektedir.

Yeni geliştirilen bu ajanlar sayesinde hem daha iyi sonuçlar elde edilmesi hem de seçilmiş hastalarda daha az toksik rejimlerle daha iyi tedaviler yapılabilmesi mümkün olabilecektir. Bu noktada en önemli konu, direnç ya da yanıt açısından yol gösterecek biyobelirteçlerin geliştirilmesi gibi durmaktadır. Halen devam etmekte olan ve ileride planlanacak klinik çalışmalar ile hem direnç mekanizmalarını belirlemede hem de bu direnç yolaklarını yenmede yeni seçenekler ortaya konulması beklenmektedir.

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