BÖLÜM 22

Metastatik İyi Farklılaşmış Gastrointestinal ve Pankreas Nöroendokrin Tümörlerde Tedavi

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Giriş

Nöroendokrin hücreler vücutta geniş bir şekilde dağılır ve bu hücrelerin nöroendokrin tümörleri (NET) olarak adlandırılan neoplazmaları birçok bölgede ortaya çıkabilir.

NET'ler, değişken ancak çoğu zaman yavaş büyüyen biyolojik davranışlarla karakterize edilen heterojen bir malignite grubudur. Klinik davranış ve prognoz, mitotik sayı ve/veya Ki-67 indeksi ile değerlendirildiği üzere histolojik farklılaşma ve derece ile yakından ilişkilidir (1).

Sınıflandırma ve Biyolojik Davranış

Dünya Sağlık Örgütü (WHO), tüm gastroenteropankreatik NET'leri farklılaşma durumu ve derecesine göre sınıflandırır. İyi diferansiye gastroenteropankreatik NET'ler, mitotik sayı ve proliferatif indekse (Ki-67) göre düşük dereceli (G1), orta dereceli (G2) ve yüksek dereceli (G3) kategorilerine ayrılır (1). Kötü farklılaşmış NET'ler, G3 nöroendokrin karsinomlarıdır.

Sindirim sistemi içinde ortaya çıkan iyi farklılaşmış NET'ler, tübüler gastrointestinal kanalda ortaya çıktıklarında, pankreasta veya gastrinoma durumunda, proksimal duodenumda ortaya çıktıklarında veya pankreas NET'leri (adacık hücresi tümörleri) durumunda geleneksel olarak karsinoidler olarak adlandırılır. Gastrointestinal NET'ler (GINET) ve pankreas NET'leri rutin histolojik değerlendirmede benzer özelliklere sahip olabilir, ancak farklı bir patogenez ve biyolojiye sahiptirler (2). Pankreatik NET'ler GINET'lerden daha kötü prognozludur (3, 4) ve antikanser ajanlara farklı yanıt verir, çoğu ajan pankreas NET'li hastalarda GINET'li hastalardan daha yüksek yanıt oranları gösterir.

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edildiği çok merkezli bir faz II denemesinde değerlendirildi (131). 2018 ESMO toplantısında sunulan bir ön raporda, genel radyografik yanıt oranı tüm iyi farklılaştırılmış NET'ler (havuzlanmış) arasında %7,4 ve GINET hastalarında %0 idi. Ancak, iyi diferansiye NET'li hastalarda stabil hastalık oranı %55,8, GI-NET'li hastalarda ise %59,4 saptanmış (132).

Programlanmış hücre ölümü 1 ligandı (PD-L1)-pozitif ilerlemiş NET'li hastalarda pembrolizumabın aktivitesi, pankreatik NET'li 16 hastayı ve GI kaynaklı pankreas dışı NET'li 25 hastayı içeren KEYNOTE-028 çalışmasında değerlendirildi. Genel olarak, pankreas dışı NET'leri olan 3 hastada (%12, %95 GA 3-31) objektif yanıt alınmış; bu hastalarda stabil hastalık oranı %60 olarak görülmüş (n = 15) (133). Pankreas NET'lerinden sadece biri yanıt vermiştir.

Pembrolizumabın aktivitesi, hastalığı ilerlemiş veya bir veya daha fazla standart tedaviyi tolere edemeyen iyi ve orta derecede diferansiye NET'li 107 hastadan oluşan bir kohortu içeren faz II KEYNOTE-158 çalışmasında da değerlendirilmiştir (134). PD-L1 ekspresyonu hastaların %16'sında tespit edilmiştir. Birincil hastalık bölgeleri pankreas (n = 40), ince bağırsak (n = 25), diğer gastrointestinal sistemler (n = 18), akciğer (n = 14) ve diğer organları (n = 10) içermiştir. Genel yanıt oranı düşük ve 4 kısmi yanıt alındığı görülmüş (%3,7) ve medyan progresyonsuz sağkalım 4,1 ay saptanmış. Pankreatik NET'li 3 hastada ve primeri bilinmeyen 1 hastada kısmi yanıtlar kaydedilmiş; yanıt veren tüm tümörler PD-L1 negatif olarak görülmüş. Yanıt veren hastalardan 2'sinin, iki yıla yaklaşan sürekli bir yanıta sahip olduğu saptanmıştır.

Vasküler endotelyal büyüme faktörü yolu inhibitörleri (35-137) dahil olmak üzere diğer immünomodülatör ajanlarla kombinasyon halinde kontrol noktası inhibitörlerini değerlendirmek için çalışmalar devam etmektedir.

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