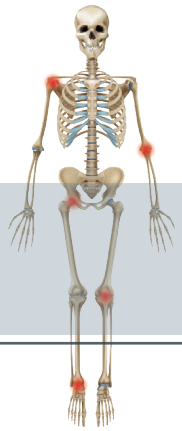
BÖLÜM 86



KEMİK SARKOMLARINDA İMMÜNOTERAPİ

Tolga SEZER [1]

GİRİŞ

Malign tümörlerin %0,2'sinden daha azı ile kemik sarkomları 'kimsesiz' tümörler olarak kabul edilir. Bu sporadik maligniteler, mezenkimal kök hücrelerin farklılaşma süreci sırasında meydana gelen onkojenik ve epigenetik olayların yanı sıra maruz kalınan mikro çevreden kaynaklanırlar. Kemik sarkomları daha çok çocukları ve genç yetişkinleri etkiler, ancak insidansı histolojik alt tiplere bağlı olarak daha yaşlı hastaları da etkileyebileceğinden gençlerle sınırlı değildir (1). Üç ana yaygın formu osteosarkom (%56), Ewing sarkomu (%34) ve kondrosarkomdur (%6). Genel olarak genç hastaları etkileyen ilk iki alt tiptir ve insidansı 15 – 18'li yaşlarda zirve yapar. Kondrosarkom ise yetişkinlerde daha yaygındır ve 40'lı yaşlarda görülme sıklığı zirveye ulaşır.

Nadir görülmelerine rağmen, kemik sarkomları yüksek bir mortalite (örneğin, osteosarkom ve Ewing sarkomunda akciğer metastazlarının gelişimi) ve/veya morbidite oranı (örneğin, kondrosarkomda yüksek lokal nüks riski) ile karakterizedir. Yeterli geniş cerrahi rezeksiyon ile birlikte osteosarkom için doksorubisin, sisplatin, metotreksat ve ifosfamid; Ewing sarkomu için vinkristin, ifosfamid, doksorubisin ve etoposid ile kombine adjuvan ve neo-adjuvan kemoterapi uygulaması bu üç tümör için merkezi tedavi prosedürünü oluşturur (2).

Yüksek dereceli kondrosarkomlar, rezeke edilemeyen tümörler, nüksler ve metastatik hastalıklar için de kullanılabilen, negatif sınırlar ve kemoterapi ile geniş eksizyon gerektirir (2, 3). Ne yazık ki, agresif terapötik ilaçlara rağmen, genel sağkalım oranı, 5 yıllık lokalize osteosarkom ve Ewing sarkomu için yaklaşık %65 ve metastazı olan hastalar için %20-30; kondrosarkom için 10 yıl sonra %50-60 oranındadır (3).

Bağışıklık sistemi, tümör hücrelerinin tanınmasını ve düzenleyici immün hücreler tarafından sıkı bir şekilde kontrol eden, spesifik efektör hücreler tarafından oluşturulan karmaşık bir biyolojik süreçtir. Buna karşılık, tümör hücreleri bağışıklık sisteminden kaçmak için faktör salınımı (örneğin sitokinler) ile hücre yüzeyinde bulunan ve kanser hücrelerinin tanınmasını sağlayan reseptör uyarımını azaltabilir.

İmmünolojik yaklaşım, ilk olarak 50 yıl önce Burnet tarafından önerilmiştir (5). Bağışıklık sisteminin tümör sürveyansının kontrolünde ikili işlevi üç aşamadan oluşur. Hassas kanser hücrelerini yok eden, doğuştan gelen ve adaptif bağı-

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Tüm kemik sarkomlarının tam moleküler profili, tümörle ilişkili yeni antijenleri aramak ve kanser hücreleri ve çevreleri tarafından ifade edilen bağışıklık kontrol noktası proteinlerinin bir listesinin histolojik alt tiplere ve derecelendirmeye göre oluşturulması için zorunludur. Birleşik Krallık'ta devam eden 100.000 genom projesi, devam eden iddialı projenin bir örneğidir. Hedeflenebilir biyobelirteçlerin listesi, hasta sınıflandırmasını iyileştirerek gelecekteki klinik gelişim için çok önemli bir adımdır. Klinik denemelerin çoğunda açıklanan immünoterapötik tepkiler, yanıt verme olasılığı en yüksek olan hastaların daha iyi tanımlanması ve ardından kaydedilen hastaların daha iyi seçilmesi lehine bir argümandır.

Son 50 yılda ilaç kombinasyonlarına dayalı terapötik yaklaşımların geliştirilmesi, genel sağkalımda gerçek bir iyileşme gösterememiştir. Son zamanlarda onkoimmünoloji, bağışıklık sisteminin onkolojik süreçte oynadığı önemli rolün daha iyi anlaşılmasını sağlamıştır. Kanser hücrelerinin tanınmasını kolaylaştırmak için bağışıklık sistemini yeniden programlamak amacıyla yapılan klinik deneylerin artışı ile kemik sarkomlarının immüninfiltratları karakterize edilmiş ve moleküler profilleri immünterapötik hedefler olarak tanımlanmıştır. Ne yazık ki, denemelerdeki klinik tepkiler, özellikle pediatrik formlarda immünoterapötik yanıtın kilidini açmak için tümör mikro-ortamının karakterizasyonunu iyileştirme gerekliliğini ortaya çıkartmıştır.

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