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İMMUNOTERAPİ İLE SİSTEMİK KEMOTERAPİNİN KOMBİNASYON TEDAVİLERİ

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GİRİŞ

İmmünoloji ve onkoloji alanları, cerrah William Coley'nin öldürülmüş bakterilerin sarkom bölgelerine enjeksiyonunun tümör küçülmesine yol açabileceğini bildirdiği 19. yüzyılın sonlarından beri gelişimleri birbirlerine bağlantılı bir şekilde devam etmektedir [(1)] . O zamandan beri, bağışıklık sistemi ile tümör büyümesi ve gelişimi arasındaki kesişimin artması, tüm kanser türlerinde geniş terapötik ilerlemelere yol açmıştır.

Kanser hastalarının tedavisinde son zamanlarda çeşitli immünoterapötiklerin uygulanması, devrim niteliğinde değişimlere neden olmuştur. Bununla birlikte, yanıt oranları hala yaklaşık % 20 ila %40 arasında sınırlı olup, kemoterapi, radyoterapi, epigenetik modülatörler ve hedefe yönelik tedaviler gibi geleneksel tedaviler ile immünoterapi kombinasyonlarının, anti-tümör bağışıklığını arttırmak için bir seçenek olabileceğini düşündürmektedir. İmmünoterapilerle kombinasyon halinde farklı immün olmayan bazı tedavilerin, bağışıklık baskılayıcı tümör mikro-ortamını yeniden programlayabileceği ve tümör hücrelerinin immünojenikliğini artırabileceği ve bunun da daha iyi terapötik etkinliğe ve hasta sonuçlarına yol açabileceği düşünülmektedir. Bu farklı terapilerin immünoterapilere eklenmesiyle elde edilen artan objektif cevapların çeşitli örnekleri olmasına rağmen, hastalar için klinik faydayı en üst düzeye çıkarmak amacıyla kontrol noktası inhibitör kombinasyonlarının rasyonel ve kanıta dayalı tedavi stratejilerine dönük çalışmalar yoğunluk kazanmıştır. Özellikle bağışıklık kontrol noktası (immune checkpoint:iCP) moleküllerine karşı oluşturulan T lenfosit antijen 4 (CTLA-4)

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infiltrasyonu ve PD-L1 gibi iCP'lerin ekspresyonu, kontrol noktası blokajı cevabı için öngörücü olduğu tartışılmıştır. Buna ek olarak, iCPI'nin diğer terapilerle kombinasyonlarının listesi geniştir ve iCPI kombinasyon terapilerinin potansiyeline rağmen, daha fazla hasta için hayatta kalma yararı sağlamak için immünoterapi kombinasyonları uygulanan hastaları seçmek için biyobelirteçleri tanımlama ve azaltılmış yan etki ihtiyacının altını çizmek gerekmektedir. Son çalışmalarda, TMB, iCPI ekspresyonu ve immün hücre infiltrasyonu, konak genetik, mikrosatellit instabilitesi, neo-antijen kaybının, TME'nın hücresel olmayan bileşimi ve mikrobiyom analizi önerilmektedir. Bu nedenle, standartlaştırılmış ve optimize edilmiş (bağışıklık) izlemenin yanısıra bağışıklık tepkisinin dinamiklerini, posttranslasyonel modifikasyonları, bağışıklık ve tümör hücrelerinin düzeni , ayrıca TME'nin, hipoksi ve pH değeri gibi fiziksel faktörler immünoterapileri uyarlamak için çok önemlidir. Bu zorlukların üstesinden gelmek ve yeni ajanların uygulanması ve kombinasyon stratejiler şu anda iCPI tedavisinde etkinliklerini artırmak ve dirençleri önlemek için ana araştırma odağıdır.

Kemoterapinin immünostimülatör etkileri hakkında çok fazla araştırma yapılmış olsada, dozaj ve program, uzun süreli bağışıklık belleği ve kemoterapi ve immünoterapi kombinasyonları söz konusu olduğunda henüz çok az şey öğrenilmiştir. Yeni kombinasyon tedavilerinin geliştirilmesi, immünoterapi uygulamalarını genişletecek ve daha erişilebilir hale getirecektir.

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