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HEMATOLOJİK MALİGNİTELERDE CAR-T CELL TEDAVİLER

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1. GİRİŞ

Kanser immunoterapisi ile verilen tedaviye tolerans gelişmesi problemini çözebilmek için, allojeneik T hücre infüzyonları, tümöral dokuyu infiltre eden lenfositlerin geliştirilmesi ile elde edilen yeni adoptif hücre (TILs) infüzyonları, immun aktivasyonun negatif düzenleyicileri olan CTLA-4 ve PD-1 inhibisyonu gibi bir dizi girişimler yapılmıştır. Toleransın üstesinden gelebilmek için geliştirilen bir strateji de; T hücrelerini kimerik antijen reseptörler (CAR) ile genetik olarak programlayarak yeniden kanser hücresine yöneltmektir [1].

2. CAR-T CELL NEDİR?

Adoptif Hücre Tedavisi (AHT) ilk defa Billingham, Brent ve Madewar tarafından allograft rejeksiyonunu, adoptif immunoterapi terimi ise malignite ve enfeksiyonları tedavi etmek için immunkompetan lenfositlerin infüzyonunu tanımlama amaçlı kullanılmıştır [2-4]. AHT'nin ilk başarılı klinik uygulamaları 1980'li yıllarda, metastatik malign melanomlu hastalarda otolog tümör-infiltre lenfositlerin ve nüks lösemili hastalarda da allojeneik donör lenfosit infüzyonlarının kullanımına dayanır [5,6]. 1990'lı yıllara gelindiğinde T hücrelerinin özgüllüğünü, T hücre yüzey reseptörü (TCR) veya CAR'leri kullanarak arttırmak için gen transfer teknikleri geliştirilmiştir [7]. Kimerik antijen reseptörler, özellikle T hücresi gibi immun efektör hücrelere yönelik olarak ex vivo tasarlanmış, T hücre fonksiyonlarını arttıran reseptörlerdir [8]. CAR-T hücreler bir defa hastaya infüze edildiklerinde, giderek

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bildirilmektedir. İlk infuzyondan 1-2 saat sonra gelişen ateş, taşikardi, hipotansiyon, hipoksi, ejeksiyon fraksiyonunda azalma, renal yetmezlik, karaciğer enzimlerinde yükselme ve koagulasyon bozukluğu (protrombin zamanı/aktive parsiyel tromboplastin zamanının uzaması) ile karakterizedir [52]. Etyolojisinde IL-6 ve TNF-α gibi sitokinler yer almaktadır, bunlar ölmekte olan B hücrelerinden, tümör hücrelerinden veya makrofajlardan salınmaktadır [53]. Tedavisinde, standart destek tedavisi ve IL-6 reseptor antagonisti olan tocilizumab veya kortikosteroidler uygulanır. Kortikosteroidler, CAR-T cell aktivitesini baskılayabileceğinden tedavide ilk tercih edilen immunosupresif ajan tocilizumab'dır [54].

Nörolojik olaylar sık görülen diğer önemli yan etkilerindendir. Nörolojik olaylar genellikle geri dönüşümlüdür. Deliryum, global ensefalopati, afazi ve nöbet ile karakterizedir. Kortikosteroidler ile tedavi edilir [29,54].

Anti-CD19/CD20 CAR-T cell tedavisinin önemli bir başka yan etkisi, B-hücre aplazisidir [29,55,56]. Bu durumda görülebilecek sık ciddi enfeksiyon riskini azaltmak için γ globülin tedavisi verilebilir [57].

CAR-T cell tedavisi sonrası görülebilen, hızlı ve masif bir şekilde hedef tümör hücresinin yıkımına bağlı olarak gelişebilen, bir diğer yan etki ise tümör lizis sendromudur [51]. Makrofaj aktivasyon sendromu; sistemik inflamatuar semptomlar ve pansitopeni bulgusu ile seyreden, mortalitesi yüksek CAR-T cell tedavisi ilişkili nadir görülen bir yan etkidir [58].

5. SONUÇ

CAR-T cell'ler gelecek vaad eden tedavi yöntemleri olarak görülmektedir. Relaps/refrakter ALL ve DBBHL'da başarılı sonuçlar alınmasının ardından FDA tarafından onaylanıp kullanıma girmiştir. AML, MM, KLL gibi bazı hematolojik malignitelerde de klinik çalışmalar devam etmektedir.

Anahtar Kelimeler: Hematolojik malignite, CAR-T cell, sitokin salınım sendromu

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