Bölüm
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MULTİPL MYELOM HÜCRELERİNİ HEDEF ALAN MONOKLONAL ANTİKORLAR

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Antimyeloma monoklonal antikolar (mAb'lar), ilaca bağlı mAb'lar ya da bispesifik antikorlara karşılık gelen, malign plazma hücrelerini hedef alan humanize edilmiş ya da kimerik antikorlardır.

CS1'İ HEDEF ALAN MONOKLONAL ANTİKORLAR

Elotuzumab, sinyal üreten lenfositik aktivasyon molekülü F7'yi (SLAMF7, CS1 [hücre-yüzey glikoproteini CD2 altgrubu 1] de denir) hedefleyen humanize edilmiş immunoglobülin G1 immüno stimülatör mAb'dir. SLAMF7 myeloma ve doğal katil (NK) hücreler üzerinde eksprese edilen bir glikoproteindir (1,2). SLAMF7, 1q23 kromozomu üzerinde yerleşmiş SLAM ailesine bir üye olup, sitogenetik anormalliklerden bağımsız şekilde Multipl Myelom (MM) hücrelerinde yüksek oranda eksprese edilir.

Elotuzumab'ın SLAMF7'ye bağlanması, adaptör proteini EAT-2 ile birleşerek NK hücrelerini aktive ederken, EAT-2 MM hücrelerinde eksprese edilmediğinden bunlarda antikor aracılı hücre sitotoksisitesine yol açar (3,4). Elotuzumab'ın tek ajan olarak relaps ya da refrakter MM (RRMM)'da makul bir etkisi vardır; 35 relaps-refrakter MM hastası içeren bir faz 1 çalışmada hastaların %26.5'inin stabil hastalığı mevcuttu ancak genel bir yanıt gözlenmedi (5). Ancak, NK hücrelerini aktive eden ve T hücre regulatörlerini inhibe eden IMid'lerin immün sistem üzerindeki etkiler düşünülerek bazı çalışmalarda Elotuzumab IMid'ler ile kombine edilmiş ve ciddi bir sinerjistik aktivite göstermişlerdir. RRMM'da Elotuzumab'ı bortezomib/dekzametazon (Dex) ya da Len/Dex ile kombine eden 2 faz I çalışmada genel yanıt oranları sırasıyla %48 ve %82 idi (6,7). Faz III klinik çalışması ELOQUENT 2'de (8), Elotuzumab RRMM'de Len/Dex'e ilave edilerek değerlendirildi. Elotuzumab grubunda genel yanıt oranı %79 iken kontrol grubunda %66 idi (P <0.001), ve elotuzumab grubunda medyan ilerlemesiz sağkalım (PFS) 19.4

İMMÜN KONTROL NOKTALARINI HEDEF ALAN MONOKLONAL ANTİKORLAR

İmmün kontrol noktası inhibitörlerinin geliştirilmesi onkolojide son birkaç yılda meydana gelen en önemli ilerlemelerden biridir. İmmün kontrol noktalarını hedefleyen mAb'lerin geliştirilmesi, melanoma, akciğer kanser, relaps ve refrakter Hodgkin hastalığı ve diğer kanser türlerini içine alacak şekilde bazı kanserlerin tedavi ve prognozunu dramatik şekilde değiştirmiştir. MM'da PD-1 reseptörü (PD-L1 ya da PD-L2) yüksek oranda eksprese olur, bu da bunun ya da bunun ligandının hedeflenmesinin etkin bir strateji olacağını göstermektedir (43). PD-1 (pembrolizumab, nivolumab) ya da PD-L1 (durvalumab, atezolizumab) hedefleyen bazı mAb'ler diğer çeşitli kanserlerde onaylanmıştır (44).

RRMM'da Pom/Dex ve Len/Dex ile pembrolizumab'ın kombinasyonunun umut vadeden faz II çalışmanın verilerine dayanarak 3 tane faz III klinik çalışma yürütülmüştür—KEYNOTE-183 ve KEYNOTE-185 ve CheckMate 602— sırasıyla RRMM'da Pembrolizumalı veya Pembrolizumabsız Pom/Dex, yeni tanı koyulmuş otolog kök hücre nakline uygun olmayan MM hastalarında Pembrolizumablı veya Pembrolizumabsız Len/Dex ve RRMM'da nivolumab artı Pom–Dex'e karşı tek başına Pom–Dex ya da Pom/Dex/elotuzumab/nivolumab kullanıldı. Her üç çalışma da Pembrolizumab alan hastalarda artan ölüm nedeniyle erken sonlandırılmıştır; ölüm için zarar oranı KEYNOTE-183'de 1.61 ve KEYNOTE-185'de 2.06'ydı; CheckMate 602'de de nivolumab için durum benzerdi (ölüm için zarar oranı 1.19; %95 GA, 0.64–2.20). Dahası, pembroziumab ya da nivolumab eklenmesi GYO'nını artırmamıştı. Önemli bir nokta, her üç çalışmada özel bir ölüm nedeni izlenmemiş olup, mAb'lerin belirgin etkinliği yanında kombinasyonun toksisitesinin arkasındaki patogenez de büyük oranda meçhuldür. Bu sonuçlar, bu ajanların MM'da en azından immünmodülatör ajanlarla kombinasyon halinde kullanılmasıyla ilgili ciddi kuşkular uyandırmıştır (45). Ancak, preklinik araştırmalarında LAG3, TIM3, ya da TIGIT gibi diğer immün kontrol noktaları incelenmektedir (46-49).

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