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Commentary

CAR T Cells: An Emerging Therapy and New Horizon in Patients with Relapsed Refractory Multiple Myeloma

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Multiple myeloma (MM) is a plasma cell disorder that originates in the bone marrow. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are two pre-malignant phases that usually precede overt myeloma. MM makes up to 10% of overall hematologic cancers [1].

Despite therapeutic advancement, MM is still incurable due to its complex nature. Additionally, substantial heterogeneity exists among MM patients [2]. Relapses (as per International Myeloma Workshop Consensus 2011) [3] occur even with immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies like anti-CD38 [1,4].

Chimeric antigen receptor (CAR) T cells are promising novel immunotherapy and are under evaluation for B-Cell malignancies. CAR T-cells are the patients' isolated T cells. They are collected and genetically engineered in the laboratory and administered back to the patients [4]. Several types of CAR T-cells exist that target different proteins and cell markers, such as B-cell maturation antigen (BCMA), CD19, etc [5]. Idecabtagene vicleucel (ide-cel or bb2121)-an anti-BCMA CAR T-cell has received first-ever US food and drug administration (FDA) approval on March 26, 2021, in MM patients who are relapsed or refractory to ≥ 4 therapy lines. That includes IMiDs, PIs, and anti-CD38 monoclonal antibodies [6].

Munshi., *et al*. reported results of the multicenter phase 2 "KarMMA" trial. Total n = 140 patients diagnosed with relapsed refractory MM who had previously received at least 3 lines of therapy were enrolled. The Ide-cel dose ranged from 150 to 450 x 106 CAR T cells. Safety and efficacy were evaluated in n = 128 patients. After a median follow-up of 13.3 months, the overall response rate (ORR) was 94/128 (73%) [95% CI, 66 to 81] with $P < 0.001$, complete response (CR) or better was n = 42/128 (33%), and very good partial response or better was 67/128 (52%). Out of 128 patients, n = 33 (26%) has achieved Minimal residual disease (MRD) negative status. Furthermore, duration of the median progression-free survivor was 8.8 months. Most common grade 3 or 4 hematologic adverse events (AEs) were neutropenia (91%), thrombocytopenia (63%), and anemia (70%). There was no significant difference in the occurrence and severity of pancytopenia and infections across the dose range. In contrast, n = 107 (84%) showed cytokine release syndrome (CRS), in which only 5% revealed grade 3 or greater [7].

The bb2121 CAR T-cell showed meaningful anti-tumor activity in heavily pretreated relapsed/refractory MM patients based on deep and durable responses with a tolerable toxicity profile. This genetically modified therapy broadens the horizon for patients suffering from relapsed/refractory MM. Similarly, multiple trials in different phases assessing various CAR T-cell types are currently underway; however, long-term safety and efficacy data evaluation is warranted for ide-cel.

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