editorial

memo (2022) 15:173–175
https://doi.org/10.1007/s12254-022-00830-9

memo
magazine of european medical oncology

CAR-T cells—Real-time experience applying CAR-T cells—What we have learned so far

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Accepted: 25 July 2022

CD19-targeted chimeric antigen receptor-engineered (CAR)-T cells are novel therapies showing great promise for patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma, mantle cell lymphoma, and follicular lymphoma. EMA-approved and commercially available CAR-T cell products have been used successfully by qualified CAR-T cell centers worldwide and these real world data compare favorably to pivotal study results with overall response rates (ORR) and complete response rates (CR) ranging from 51–93% and 40–64%, respectively [1–9].

Recently, axicabtagene ciloleucel (axi-cel) received FDA approval based on results of a multicenter, randomized study comparing axi-cel to conventional salvage chemoimmunotherapy and autologous blood stem cell transplantation (ASCT) as second-line treatment in patients with relapsed or refractory DLBCL [10, 11]. After a median follow-up of 24.9 months, median event-free survival (EFS) was more than 4-fold greater and ORR was 33% higher with double the CR rate in the axi-cel arm. Nearly three times the number of patients in the axi-cel arm received definitive therapy compared to the control arm (94% vs 36%), respectively.

CAR-T cell therapy targeting B cell maturation antigen (BCMA) has been approved by the FDA and EMA for treatment of patients with relapsed and refractory multiple myeloma (MM) based on high ORR of 82–98% and median progression-free survival (PFS) between 12 and more than 24 months [12, 13]. Unfortunately, these adoptive immunotherapies, so far, have not been available in Europe due to limited production capacities of established CAR-T cell facilities and commercial interests.

As cellular products, CAR-T cells are associated with unique toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [14, 15]. Recognition, management, and differentiation of CAR-T cell toxicities are crucial for safe and broad employment of this therapy. Real world data confirmed the well-known adverse reactions of CAR-T cells and in some analyses lower severe CRS and ICANS rates were reported most likely due to the fact that clinical experience improved their early detection [6–9]. Furthermore, use of corticosteroids to mitigate toxicities by inhibiting the proliferation and/or inflammatory cytokine production from CAR-T cells and other immune cells has become more liberal with initiation at lower grades of CRS or ICANS [6, 7]. More frequent use of CAR-T cells in the real world resulted in detection of so far, unexpected and unreported side effects such as cardiomyopathy, hepatic failure, and gastrointestinal perforation [9]. Limited reports demonstrated a low rate of secondary malignancies (SMNs) after CAR-T cell therapy; however longer follow-up times are needed to properly evaluate the cumulative incidence and type of SMNs, respectively [16, 17].

Patient selection and the ability to successfully collect T cells and generate an effective product are key factors to be considered by patients and physicians pursuing use of CAR-T cells [18, 19]. Patient-related factors (e.g., ECOG performance score and comorbidities), disease-related factors (e.g., relapsed/refractory status, tumor burden, extranodal sites, and LDH elevation), treatment-related factors (e.g., number and intensity of prior lines of therapy, bridging therapy until CAR-T cell infusion and lymphodepleting chemotherapy as well as quantity and quality of

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leukapheresed T cells) may influence optimal outcomes after CAR-T cell therapy. Current research focuses on improving various aspects, including CAR-T cell proliferation and persistence, their killing potential in an immunosuppressive tumor environment, and target antigen expression. Relapses associated with the loss of target antigen following CAR-T cell administration have led to investigation of alternative tumor-specific targets, targeting of multiple antigens with a single CAR-T cell (tandem CAR), incorporation of a cytokine-induced domain (TRUCKs, T cells redirected for universal cytokine mediated killing), and incorporation of on/off switches or suicide genes to the CAR constructs to avoid severe toxicities [20, 21].

Adoptive CAR-T cell therapies are highly effective treatments for certain patients with hematological malignancies. However, further basic research regarding CAR constructs and ways to overcome the immunosuppressive tumor microenvironment as well as clinical trials are needed to improve therapeutic results, increase durability of responses, and reduce side effects of therapies. With more data accumulating in the real-world settings, a wider range of different bridging approaches being used, and incorporation of CAR-T cell therapies earlier in the disease course, patient outcomes will further improve. All these efforts will hopefully lead to a safe, effective, and financially available adoptive immunotherapy as standard for all patients in need.

Conflict of interest H. Greinix: Honoraria for participation in speakers bureau and advisory boards from Gilead, Novartis, Celgene, Sanofi, Takeda, and Therakos.

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