CAR T-cell treatment of high-risk multiple myeloma: will there be a cure?

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Multiple myeloma (MM) is a cunning disease. Despite enormous progress in its treatment, cure is uncommon. Not long ago, some of the most important researchers in the field seemed to be happy if it could be turned into a chronic disease. Others went for cure.

The first attempts to cure the disease included autologous[1] and allogeneic[2] transplants after high-dose myeloablative treatment. Occasional patients survived 20 years or more, mainly following allogeneic transplantation. The idea that high-dose treatment was not the most important part of the allogeneic approach, but rather the graft-*versus*-myeloma effect exerted by the transplanted allogeneic lymphocytes, induced a modification of the procedure using a reduced intensity conditioning and a preceding auto-transplant.[3] Results were encouraging, but relapses continued to occur, and cures were rare. Donor lymphocyte transfusion to treat relapses were successful in the short term[4,5] and were proof of principle that cell therapy with allogeneic lymphocytes could induce responses lasting for several months or even years.

However, the relatively short-term donor lymphocyte effect was unspecific and frequently caused graft-*versus*-host disease. Thus, the real breakthrough was creating a lymphocyte, i.e., a T lymphocyte, that could target specific antigens on the tumor cells. An effective chimeric antigen receptor (CAR) T cell had already been produced in the early 1990s,[6] and, after some delay, CAR T cells for clinical use were developed. From the beginning of the 21st century until now, the number of clinical cancer trials with such cells has exploded.

In MM, the most common target for CAR T cells has been B-cell maturation antigen (BCMA), but many other antigens on myeloma cells are currently being explored as targets. CAR T cells are T cells modified *ex vivo* to express a chimeric receptor. This receptor contains an antigen receptor, i.e., a single chain variable fragment (scFv), and an intracellular T-cell receptor (TCR) signaling domain. The scFv recognizes the target tumor cells, while the intracellular domain contains various components to enhance efficacy and safety. In most of the ongoing studies, autologous cells are used for CAR T-cell production.

Two such CAR T-cell products have been approved for treatment of MM by both the US Food and Drug Administration and the European Medicines Agency, based on two phase II studies including 128 patients treated with ide-cabtagene vicleucel (ide-cel)-KarMMa,[7] and 97 treated with ciltacabtagene autoleucel (cilta-cel)-CARTITUDE,[8] respectively. Both trials have shown impressive results in triple-penta refractory patients with a median of six lines of previous treatment. A recent updated retrospective comparison has shown superior response (objective response rate 97.9%; stringent complete response 82.5%), progression-free survival (PFS) (62% reduction in risk), and overall survival (OS) (57% reduction in risk) with cilta-cel as compared to ide-cel.[9] Other studies including fewer patients have also shown impressive results short term.

Although these results are encouraging, the number of patients investigated in each of the studies is not high enough to provide reliable information of the impact of prognostic factors such as presence of extramedullary disease or high-risk cytogenetics.

In the present issue of *Haematologica*, Gagelmann *et al.*[10] attempt to analyze these important prognostic factors retrospectively by compiling results from available CAR T-cell clinical trials. Out of 769 screened articles, they found 17 including 723 patients with heavily pre-treated relapsed or refractory MM patients with data including enough information about these prognostic factors. A comprehensive statistical analysis was able to conclude that extramedullary disease (EMD) did not hamper response, but PFS was decreased by 44% and OS was shorter due to EMD. Cytogenetic high-risk patients did even worse in comparison to the non-high-risk patients. The risk of no response was increased by 14%, the risk of minimal residual disease positivity by 23%, and the risk of progression/relapse was increased by 70%, affecting the OS that was significantly shortened.

Thus, it seems that CAR T-cell treatments currently in use do not overcome the poor prognostic impact of EMD or high-risk cytogenetics; new approaches are, therefore, warranted. In most of the included patients, BCMA was the target for the CAR T cells and autologous cells were used. Ongoing studies using CAR T cells directed against other antigens, such as the orphan G protein-coupled receptor, class C group 5 (GPRC5),[11] bidirected CAR T cells, allogeneic CAR T cells, natural killer (NK) cells[12] or CAR NK cells may show better response and outcome for high-risk relapsed and refractory myeloma patients. Future studies should move CAR T-cell treatment to an earlier stage of the disease. Myeloma with EMD and high-risk cytogenetics may well be treated up front with CAR T-cell therapy, and responses consolidated with other treatments, such as bispecific antibodies or allogeneic transplants. The goal must be cure.

Disclosures

GG is Advisor to the Fujimoto Pharmaceutical Corporation, Japan, and has received honorarium from them. In 2022 GG received honorarium from an interview with BMS. GG has shares in a small innovation Karolinska Institutet associated company called XNK (with no value on the market). GG has shares in Astra Pharmaceuticals.

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