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

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Multiple myeloma 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 and allogeneic 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 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. Results were encouraging, but relapses continued to occur, and cures were rare. Donor lymphocyte transfusion to treat relapses were successful in the short term 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-lymphocytes, that could target specific antigens on the tumor cells. An effective chimeric antigen receptor (CAR) T cell was produced already in the early 1990th 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 multiple myeloma the most common target for CAR-T cells has been B cell maturation antigen (BCMA), but many other antigens on myeloma cells are currently 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 present studies autologous cells are used for CAR-T cell production.

Two such CAR-T cell products have been approved for treatment of multiple myeloma by both by FDA and EMA, based on two phase II studies including 128 patients treated with Idecabtagene vicleucel (ide cel) - KarMMa, and 97 treated with Ciltacabtagene autoleucel (cilta cel) - CARTITUDE respectively. Both trials have shown impressive results in triple - penta refractory patients with a median of 6 lines of previous
A recent updated retrospective comparison has shown superior response (ORR 97.9%, sCR 82.5%), PFS (risk reduction of 62%) and OS (risk reduction of 57%) with cilta-cel as compared to ide-cel\(^9\). Other studies including fewer patients have also shown impressing results short term.

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

In the present issue of Haematologica Gagelmann et al\(^{10}\) attempts to analyze these important prognostic factors retrospectively by compiling results from available CAR-T clinical trials. Out of 769 screened articles they found 17 including 723 patients with heavily pretreated relapsed or refractory multiple myeloma patients with data including enough information about these prognostic factors. A comprehensive statistical analysis could conclude that extramedullary disease (EMD) did not hamper response, but progression free survival 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 with 14%, the risk of MRD positivity with 23 % and the risk of progression/relapse was increased with 70%, affecting the overall survival that was significantly shortened.

Thus, it seems that presently used CAR-T cell treatment does 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 cell were used. Ongoing studies using CAR-T cells directed against other antigens like the orphan G Protein-coupled receptor, class C group 5 (GPRC5)\(^{11}\), bidirected CAR-T cells, allogeneic CAR-T cells, 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, and responses consolidated with other treatments like bispecific antibodies or allogenic transplants. The goal must be cure.
References: