MultipleMyelomaHub

General MM, Patients eligible for transplant, Elderly patients, Patients non-eligible for transplant, Relapsed/refractory patients

CAR T Cell Meeting 2019 | CAR T in multiple myeloma: when to use CAR T

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On February 14, 2019, Professor Hermann Einsele, University Hospital Würzburg, Germany, presented at the 1st European CAR T Cell Meeting in Paris, France, on the topic of when to use chimeric antigen receptor T-cell (CAR T) therapy in multiple myeloma (MM). Professor Einsele, one of the MM Hub's steering committee members, discussed when CAR T therapy may be appropriate in the MM treatment pathway, why T-cell redirection strategies fail and the future of CAR T in MM. In this article, the MM Hub have summarized the key information from Professor Einsele's talk.[1]

The treatment pathway and therapies under investigation

The treatment of MM begins with induction therapy and is then divided by the patient's eligibility to undergo an autologous stem cell transplant (ASCT). Patients who are eligible for ASCT then undergo consolidation and maintenance whilst those who are ineligible have continuous therapy, continuing until relapse.

In elderly, newly diagnosed MM (NDMM) patients who are ineligible for transplant, there are ongoing phase III trials investigating the use of a traditional doublet or triplet regimen (containing a proteasome inhibitor [PI] and/or immunomodulatory drug [IMID]) with the addition of a monoclonal antibody (MAb). Elotuzimab is being investigated in the Eloquent-1 study (NCT01335399) whilst ALYCONE (NCT02195479) and MAIA (NCT02252172) are evaluating the addition of daratumumab.

The addition of the MAb to these regimens has improved the response rate and the duration of response (DoR), as well as progression free survival (PFS). This has been shown in the Alycone study where daratumumab is added to the triplet; bortezomib, melaphalan and prednisone (VMP).[2] In these patients, it is now believed a PFS of 3–4 years could be achieved, with other salvage options providing further benefit. However, it is still difficult to control the disease despite the addition of novel agents.

Meanwhile, in the younger, transplant eligible patients, there are a minority that achieve a complete response (CR), especially following ASCT. One study by Joaquin Martinez-Lopez and colleagues has shown a PFS up to 20 years, with 35% of patients still in CR at a median follow-up of 17 years. These results are significant considering the trial has not involved any novel agents.[3]

To investigate how the addition of novel agents can improve on the results by Martinez-Lopez and colleagues, the recent results of the Gimema-MMY-3006 (NCT01134484) study can be analyzed. In this phase III study, the triplet of bortezomib, thalidomide and dexamethasone (VTD) was given as induction therapy before and consolidation therapy after double ASCT in patients with NDMM. They compared VTD to thalidomide-dexamethasone (TD) alone. Their results, with a long follow-up of 10-years demonstrated a PFS of 34% and an overall survival (OS) rate of 60%.[4]

Therefore, the novel regimens used now in this setting are usually triplet therapies with the addition of a MAb such as VTD with daratumumab. In the DSMM XVII study (2017-001616-11) in Germany, the four-drug combination of elotuzimab, carfilzomib, lenalidomide, dexamethasone (E-KRd) as induction and consolidation is being investigated in 580 patients with a goal of a 10-year PFS.

Where is the unmet need?

A study by Brian A. Walker and colleagues demonstrated patients with high-risk and ultra high-risk (Double Hit) cytogenetics had a significantly shorter PFS compared to patients with standard risk disease.[5] These patients may represent ideal candidates for upfront immunotherapy with CAR T cells.

Another subset of patients who may benefit from CAR T therapy are those who relapse early following ASCT. A study by Ajay Nooka and colleagues showed that patients who relapsed after modern induction therapy such as lenalidomide, bortezomib and dexamethasone (RVD) plus high-dose melphalan with ASCT have poor outcomes with a PFS of approximately two years.[6]

Lastly, the cohort of heavily pretreated patients may make ideal recipients of CAR T-cell therapy as they have a poor prognosis and the DoR of each subsequent treatment decreases with each line of therapy.[7]

Where might CAR T therapy be indicated in MM?

1. In patients who are not eligible for transplant, CAR T may consolidate or maintain remission, however safety is a concern
2. In patients who are eligible for transplant there are two main groups who may benefit – those with adverse cytogenetics and those who progress early following ASCT. In both populations CAR T may consolidate or maintain remission, but the long-term efficacy needs to be shown
3. Heavily pre-treated patients (double–penta refractory) may also obtain some benefit but the efficacy of CAR T in this population must be shown with MRD-negativity for prolonged PFS

The new goals of treatment

Minimal residual disease (MRD)-negativity is increasingly important. Patients with an MRD-negative state appear to have the same prognosis, regardless of whether they have standard or high-risk disease. The issue with this is that whilst MRD-negativity can be achieved in around 50% of patients with standard risk disease, this figure is significantly lower in those with high-risk features (for example patients with t(4;14) or del(17p).[8] Therefore, the aim should be to increase the rate of MRD-negativity in high-risk patients. Whilst adding daratumumab can increase rates of MRD-negativity and improve PFS, this is still within a subset of patients and cannot overcome the adverse cytogenetics. CAR T therapy therefore may be beneficial as a consolidation therapy based on their long persistence and potentially could replace maintenance therapy.

CAR-T Pipeline in MM

There are several immunotherapy targets for CAR T cells in MM with ongoing clinical trials investigating anti-CD19, anti-CD138 and anti-BCMA CAR-T cells with others targeting SLAMF7, CD38 and CD44v6-CAR in the preclinical stages.

In the bb2121 trial, heavily pretreated patients were enrolled and received anti-BCMA CAR T-cells. The toxicity profile was milder than in the lymphoma CAR T products and at the highest dose of >150 x 10^6 there was a 95.5% ORR with 50% CR. A median PFS of 17.7 months was also seen in 16 patients who were MRD-negative.[9] These results are impressive given the length of the PFS reported in this heavily pretreated population.

Another ongoing trial is the LEGEND-2 (NCT03090659) study, using LCAR-B38M, which has two BCMA-targeting domains leading to high avidity binding and making it unique in the anti-BCMA CAR T market. These patients were less heavily pretreated (median lines of prior therapy: 3) than the bb2121 study. The toxicity profile was consistent with other BCMA targeted CAR T cell therapy with cytokine release syndrome (CRS) ≥grade 3 experienced by 7% of patients and neurotoxicity in 2%. With an average 12-month follow up, in 57 patients, the median DoR was 16 months (95% CI, 12–not reached [NR]) and increased to 22 months (95% CI, 14–NR) in MRD-negative patients.[10] *The recent results of the LEGEND-2 trial were covered on the MM Hub and can be viewed here.*

Current CAR T trials in MM have shown an improved safety profile when compared to the lymphoma setting with lower CRS and neurotoxicity rates. Additionally, even in heavily pretreated group of patients, there is a high rate of CR/MRD-negativity.

Why might CAR T cells fail and how can we counteract this?

Lack of persistence:

- Select for the combination of CD4 and CD8 T cells
- Select for stem memory T cells
- Create a fully human CAR to reduce immunogenicity
    - A study (NCT03430011) evaluating JCARH125 - a fully human binder with a low affinity for surface BCMA with a modified spacer to increase binding to BCMA – is ongoing
    - Making these CARs less immunogenic improves the ORR

Immune escape:

- Increase expression of the target antigen
    - Gamma secretase inhibitors increase BCMA expression on the cell surface[11]
    - Histone deacetylase inhibitors have also been shown to increase the expression of the target antigen in the myeloma cell
- Target additional antigens:
    - CARAMBA study: phase I/IIa study in the relapsed setting using a SLAMF7 CAR T product
    - EURECART study: investigating the use of a CD44v6 CAR T cell product to treat advanced MM and acute myeloid leukemia
    - Xiaolan Shi and colleagues presented updated data at ASH 2018 where they used both anti-BCMA and anti-CD19 CAR T in patients with high-risk, heavily pretreated MM. They showed MRD-negative status can be achieved in this dual approach, despite the high-risk features of the patients they were treating. This approach also showed a high efficacy with over 50% CR rate and a manageable safety profile[12]

Based on these results, it could be argued that CAR T therapy should be moved into an earlier line of therapy as using CAR T upfront in high-risk patients has shown impressive efficacy results.

Other causes for CAR T cell therapy failing include malignant stem cells expressing different surface antigens in the bone marrow (which is rare) and also the upregulation of inhibitory receptors. All of these resistance mechanisms are more pronounced in patients with a higher tumor load.

What is the future of CAR T therapy in MM?

If the toxicity profile can be shown to be acceptable, then CAR T may be feasible for elderly patients who are ineligible for ASCT as an upfront consolidation therapy and potentially maintenance therapy. Beyond the second-line, whilst CAR T has been shown to be effective and provide a prolonged PFS, the cost benefit ratio needs to be analyzed. For patients who relapse early following ASCT and those with high-risk cytogenetics, CAR T may provide a long term PFS improvement and potentially cure. However, it will be important to see how competitors to CAR T therapy such as immunotoxins and bispecific antibodies perform in trials.

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