IMW 2019 | Overview of novel cellular therapies in MM

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The application of immunotherapy for the treatment of patients with hematological cancers is rapidly growing and remains the focus of many studies. During the 17th International Myeloma Workshop (IMW) in Boston, US, a number of abstracts outlining novel research on cellular therapies, alternative to CAR T cells, were presented at a session dedicated to immunotherapeutic approaches in multiple myeloma (MM). The article below summarizes the talks given by Jooeun Bae from Dana Farber Cancer Institute, Boston, US; Julie O’Neal from Washington University School of Medicine, Washington, US, and Elena Maroto-Martin from Hospital Universitario 12 de Octubre, Madrid, ES.

Combining cancer vaccine with immune checkpoint inhibitors

Jooeun Bae and co-authors characterized immune-mediated and regulatory cells in patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (SMM), and active MM. They looked at the levels of different T-cell subsets, myeloid-derived suppressor cells (MDSC), CD4⁺ regulatory T cells (T_{reg}), primary CD138⁺ myeloma cells, as well as their expression of immune checkpoint and co-stimulatory molecules. They aimed to further examine the contribution of the tumor microenvironment to the regulation of tumor-specific responses and use this knowledge to improve the efficacy of the multi TAA-specific memory CD8⁺ cytotoxic T lymphocytes (CTLs).

Bone marrow mononuclear cells (BMMCs) or peripheral blood mononuclear cells (PBMCs) of all active MM patients, independent on the stage of disease, showed increased levels of G-type MDSCs (CD11b⁺CD33⁺HLA-DR_{low}CD14⁻CD15⁺), T_{regs} (CD3⁺CD4⁺/CD25⁺FOXP3⁺), and decreased CD4⁺ T helper (T_H) cells, compared to patients with pre-malignant MGUS/SMM or healthy donors. Moreover, BMMCs and
PBMCs of patients with active disease had enhanced expression of PD1 on CD4\textsuperscript{+} T\textsubscript{h} and CD8\textsuperscript{+} CTLs. Simultaneously, CD138\textsuperscript{+} cells, G-type MDSC and CD4\textsuperscript{+} T\textsubscript{regs} isolated from BMMCs and PBMCs more frequently expressed PD-L1, similar to CD4\textsuperscript{+} T\textsubscript{regs} of patients with MGUS and SMM.

In order to address the observed increase in immune regulatory cells and upregulation of checkpoint inhibitors, the authors evaluated the impact of the addition of checkpoint inhibitor or immune agonist on the anti-tumor activity of the XBP1/CD138/CS1-specific CTL in vitro. The simultaneous blockade of PD1, LAG3, or TIM3 showed an enhanced cytotoxic activity against myeloma cells, suggesting benefits of the cancer vaccine and immune checkpoint inhibitor combination.

**BCMA-iNKT CAR cell therapy\textsuperscript{2}**

B-cell maturation antigen (BCMA), critical for cell survival, is expressed by most MM cells independent of disease stage, mutation, and chromosome status, while its expression on normal cells is restricted to plasma cells.\textsuperscript{3} Therefore, unsurprisingly, several BCMA-targeted therapies are currently in clinical trials, including antibody-drug conjugates, bi-specific antibodies, and chimeric antigen receptor (CAR) T-cell therapies. Unfortunately, responses to the CAR T cells against BCMA in patients with MM are transient and associated with increased risk of cytokine release syndrome and neurotoxicity.\textsuperscript{2} Julie O'Neal and colleagues conducted a study exploring whether toxicity could be reduced by expressing CAR proteins on invariant natural killer T cells (iNK Ts) and the efficacy enhanced with long-acting IL-7 (NT-I7) co-expression.

These cells can recognize glycolipids presented on the major histocompatibility complex-like molecule CD1d and do not cause graft-versus-host disease (GvHD).\textsuperscript{2} Therefore, iNKT-CARs could recognize and kill cells simultaneously expressing BCMA and CD1d, thus increasing efficacy whilst minimising potential toxicity. BCMA-iNKTs-CAR cells were generated from iNK Ts isolated from normal human PBMCs stimulated with matched donor irradiated negative fraction PBMCs. The authors tested the hypothesis in NOD scid gamma (NSG) mice engrafted with MM tumors treated for 28 days with either:
• 1x10^7 BCMA-iNKT-CAR - vehicle or NT-I7 (10mg/kg)
• 1x10^7 CD19-iNKT-CAR - vehicle or NT-I7 (10mg/kg)

The median survival of mice was higher in the group receiving BCMA-iCAR vehicle therapy compared to CD19-iNKT-CAR (163 days versus 45 days). Additionally, seven out of ten mice survived >200 days after receiving BCMA-iNKT-CAR-NT-I7, with no tumors detected by bio-layer interferometry. Only BCMA-iNKT-CAR-NT-I7 were detected in the blood and they showed long-term functionality when re-challenged with MM.1S-CG cells. In these re-challenged mice, while control and vehicle-treated mice had a high tumour burden, two out of four mice treated with NT-I7 were tumor-free within 5 weeks.

This efficacy of BCMA-iNKT-CAR demonstrated in vivo, as well as the enhanced expansion and survival of those cells with the addition of NT-I7, show that iNKTs can be an alternative source of off-the-shelf CAR cell therapies. Further studies are needed to optimize expansion, transduction, and vector design, as well as directly compare iNKT, CAR T, and MK-CAR therapies.

**NKG2D and BCMA-CAR NK-92 cell therapy**

Another approach, using NK cells as a source for cellular therapy, was presented by Elena Maroto-Martin. CAR-NK compared to CAR T cells have a lower probability of long-term adverse events and risk of GvHD, but also exhibit CAR-independent activity via the NK cells native receptors. Moreover, MM progression is associated with an immunosuppressive microenvironment leading to NK cell dysfunction that can be overcome by infusion of functional NK cells. Therefore, the investigators designed a study aiming to generate and compare two novel CAR-NK-92 products, targeting NKG2D or BCMA as potential candidates for the treatment of MM.

NKG2D is a non-immunogenic activating receptor, whose ligands (MICA, MICB, and UL16-binding proteins) are expressed on 85% of tumors, but not healthy tissue. While, as described above, BCMA is expressed on almost 100% of MM tumors. The authors transfected NK-92MI cells using a lentiviral vector with sequences encoding for the NKG2D receptor or a single-chain variable fragment against BCMA. Both
vectors included the same 4-1BB co-stimulatory domain and the CD3-ζ signaling domain. Transfected cells were then fluorescence-activated cell sorted to obtain stable cell lines expressing the vectors. These were then used in various cellular assays, which demonstrated the specificity and effectiveness of the CARs that were not affected by pathological levels of soluble MICA present in MM patients or clinical irradiation dose.

The data also demonstrated an association between the expression of the target ligands and the efficacy of both CAR-NK-92 products. Interestingly, both were equally efficient against cell lines that equally express BCMA and NKG2D ligands. Additionally, pre-conditioning with bortezomib increased expression of NKG2D ligands in the MM bortezomib-resistant cell line. Therefore, indicating the potential benefit with bortezomib plus NKG2D-CAR NK-92 cell infusion in patients with relapsed or refractory (R/R) MM. Importantly, both CAR-NK-92 products showed increased cytotoxic activity against primary plasma cells of patients with R/R MM compared to parental cell lines but spared PBMCs from healthy donors.

Altogether, the authors demonstrated the feasibility of these off-the-shelf CAR-NK-92 therapies for the treatment of patients with MM, including the high-risk R/R population. However, they acknowledged that an in-depth characterization of these novel CARs is needed before they can enter the next stage of clinical development.

References:


