ASH Annual Conference 2019

Orlando, Florida

I had the pleasure to attend to ASH 2019, an exciting scientific and clinical conference that brought together the most innovative scientific ideas from the field. In addition to its excellent scientific programme, the conference was packed with educational opportunities for trainees, pharmaceutical and biotech booths, privately-sponsored events and social media hubs.

Novel therapeutic technologies - such as *gene editing* and *CAR-T cell therapy* - were the highlight of the conference, which was rich in pre-clinical and clinical studies aimed to consolidate the use of these technologies in Haematology. Sickle cell and other genetic disorders are being tackled using gene therapy strategies on hematopoietic stem cells, while haematologic malignancies are relying their hopes on CAR-T cell development. Considering the recent approval of anti-CD19 CAR T cells that are now commercially available for DLBCL, NHL and paediatric B-ALL patients (Kymriah® and Yescarta® products), several real world data studies were presented and a major hit at the conference, starting to show the real long-term benefit of these strategies to haematologic patients. Following this trend, Multiple Myeloma was one of the highlights of ASH, with surprising and exciting pre-clinical and clinical studies using next-generation anti-BCMA CAR T cells for relapsed and refractory patients.

The use of anti-BCMA CAR T cells for relapsed refractory Multiple Myeloma (rrMM) patients generated promising data in the past years, with strong overall response rates across products. However, the majority of the treated patients relapse after 18 months. Therefore, it was with no surprise that ASH 2019 was packed with new anti-BCMA CAR T cell designs and novel strategies to overcome the lack of long-term efficacy and persistency of CAR T cells in Multiple Myeloma (MM). In terms of clinical studies, there were four major highlights: 1) bb21217 is a new BCMA-CAR T cell product from Bluebird Bio/Celgene, with the same CAR construct as bb2121, but using the PI3K inhibitor bb007 during the manufacturing process that enriches for a memory-like phenotype. In this dose escalation study with 38 rrMM patients, the median response rate was 11.1 months for the lowest dose ($150x10^6$ CAR^+ cells); 2) JNJ-4528, the anti-BCMA CAR T cell product from Johnson & Johnson, has two BCMA binding sites and is enriched for effector memory T cells. Their clinical trial, CARTITUDE-1, enrolled 29 patients and achieved a complete response rate in 69% (at 1 month), with 27 out of 29 patients being progression-free at 6 months post-infusion; 3) BM38 CAR T cells - a bi-specific product targeting BCMA and CD38 simultaneously, from Cellyan Therapeutics, has been infused in 22 patients and resulted in progression-free survival of 79% at 9 months (with more than 80% of the patients being MRD negative). 4) A new dose-escalation study from Fred Hutchinson Seattle, combining the use of anti-BCMA CAR T cells with prior and repeated infusions of a gamma secretase inhibitor. This clinical trial just completed the first dose of $50x10^6$ CAR^+ cells and aims to increase the BCMA exposure on the MM cell surface and reduce MM relapse. These novel studies are innovative and promising compared to the published data, as they try to overcome the lack of persistence and long-term efficacy of anti-BCMA CAR T cells in MM. However, long-term follow up data will be necessary to fully compare the products and confirm long-term benefit for MM patients. Interestingly, Adam Cohen (from UPenn) showed that different anti-BCMA CAR T cell profiles can be identified from responder

and non-responder MM patients, with responders showing a more naïve and central memory phenotype, lower Granzyme B and lower expression of the exhaustion markers.

In terms of novel pre-clinical developments for the treatment of MM, the highlight goes to an elegant work (from MSK) testing the efficacy of anti-BCMA and anti-GPRC5D CAR T cells in a MM mouse model. The bicistronic product JCARH-125 (with both CAR constructs being expressed in the same T cell) was the most efficient in eliminating MM growth, even in the presence of $BCMA^{neg}$ MM cells, and is due to be tested in a clinical trial next year. Anti-BCMA-CD3 Bites - which are antibodies that bind both the cancer cells and the T cells to promote cell engagement and MM killing - are also showing promising results in the clinic. AMG701 was presented (from Dana Farber) as an upgraded version of AMG402, and it shows a longer serum half-life and engagement of central memory and stem cell memory T cells. In the poster sessions different bispecific constructs were also presented, combining anti-BCMA with anti-CD38 or anti-CD19 antibodies, to target myeloid suppressor cells and MM progenitor cells within the bone marrow niche. Novel cell therapy platforms were also explored, such as allogeneic anti-BCMA CAR T cells produced from healthy donor volunteers (from KCL), as well as, NK-based cell therapies. The development of a personalized dendritic cell vaccine using tumour peptides is also being tested in MM patients. Some clinical trials are planned to start fairly soon (at Beth Israel and MSK), combining personalized MM vaccines with either the checkpoint inhibitor nivolumab or anti-BCMA CAR T cells.

Another important topic in MM research that was covered at ASH 2019 was the bone marrow (BM) microenvironment and how it affects the therapeutic efficacy against MM cells. The use of single-cell technologies to study the MM microenvironment was largely explored during the conference. One group used single-cell genomics to study the mesenchymal stromal cell compartment in BM biopsies from MM patients and found that MM patients have two unique MSC sub-populations, which are enriched for inflammatory and myeloma supportive genes and are absent in healthy volunteers. Another group used single-cell approaches such CYTOF and 10x genomics to investigate the lymphoid compartment of MM patients, after treatment with pomalidomide, and identified that the patients' T cells become more effector and exhausted after therapy. A third group used CYTOF to investigate whether differences in the BM microenvironment - at diagnosis - can predict the response to different MM treatments. Another group investigated the transcriptional profile of plasmacytoid dendritic cells after exposure to MM cells, and discovered that these BM microenvironmental cells promote the expression of CD73 on the surface of MM cells, blocking T cell-mediated cytotoxicity of autologous T cells. Finally, an interesting study explored the impact of BM mesenchymal stem cells (MSC) on the efficacy of different anti-CD138, anti-CD38 and anti-BCMA CAR T cells against MM cell lines, and showed that some CAR T cell products are dramatically affected by the presence of BM MSCs.

In conclusion, the field of CAR T cell therapy in Multiple Myeloma is evolving very quickly with the hope that it will bring long-term benefit for MM patients. ASH 2019 brought together all the scientific innovation and technical efforts that are being done around the world to improve the current paradigm and therapeutic options for MM patients.

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