



MPE | MYELOMA
PATIENTS
EUROPE
CONFERENCE REPORT

4th European CAR T-cell Meeting



4th European CAR T-cell Meeting

The European Hematology Association (EHA) and the European Group for Blood and Marrow Transplantation (EBMT) jointly organised the 4th edition of the European CAR T-cell Meeting. The meeting was held virtually on February 10-12, 2022. Michael Hudecek (Germany) and Ibrahim Yakoub-Agha (France) chaired the meeting. It delivered a strong programme which included CAR-T products, clinical and pre-clinical novel data, as well as therapy updates and patients' experiences.

CAR-T cells represent the promise of an unprecedented response rate, depth and length, which is effective in high-risk patients and those with extramedullary disease, and a one-off therapy followed by treatment-free interval. It does not come without risks (cytokine release syndrome (CRS), neurological syndromes, infections, prolonged cytopenias) and there is still uncertainty regarding remission length, long-term immunosuppression, efficacy at earlier lines of therapy, improvability and outcomes of relapse. The challenge: triple class refractory patients have a progression-free survival (PFS) of 4-5 months and an overall survival (OS) of 12 months with current standard of care regimens. The use of CAR-T therapies leads to better outcomes, but relapses continue to occur and long-term outcomes are uncertain. BCMA-targeted CAR-T therapies showed good results with manageable side-effects and there are research groups working on improving its efficacy. Other ways could involve using CAR-T at earlier lines of therapies, using different targets and/or allogeneic CAR-T cells. Mechanisms of resistance also need to be better understood.



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1. APPROVED THERAPIES

Hermann Einsele (Germany) gave a summary of the approved and emerging CAR-Ts in multiple myeloma (MM). He emphasised the unmet clinical needs for patients experiencing early relapse after initial therapy, high-risk patients and patients refractory to PIs/IMiDs and CD38 monoclonal antibodies. He talked about the approval of the first European myeloma CAR-T cell product targeting BCMA (Abecma/ide-cel) in 2021 and that the second product (cilta-cel, also targeting BCMA) should be approved for RRMM patients in 2022. According to the KarMMa studies, Abecma led to an overall response rate (ORR) >80% with a progression-free survival (PFS) of around 1 year. With cilta-cel, >80% of the patients, who had a median number of previous lines of therapy of 6, had a stringent complete response (sCR), with a PFS >2 years. However, high-risk patients and those with extramedullary disease had less good responses. Dr. Einsele believes that some solutions could be to improve T cells fitness and to take these products at earlier lines of therapy. CAR-T therapy will become a first-line option for ultra/high-risk patients and might challenge autologous stem cell transplant (ASCT) in transplant-eligible newly-diagnosed patients. CAR-T therapy might come at earlier lines of therapy in transplant-ineligible patients as well.

2. THE CURRENT CAR-T LANDSCAPE

Kwee Yong (UK) gave an update on several CAR-T commercial products as well as ongoing investigational products.

2.1. BCMA-targeted CAR-T

BCMA is overexpressed in plasma cells, promoting proliferation and survival of myeloma cells. This is why several commercial and investigational CAR-T therapies target this antigen: two commercial products, ide-cel (KarMMa trials) and cilta-cel (CARTITUDE trials), and other products including ARI0002h (Spanish academic trial), P-BCMA-101 (PRIME trial), Zevor-cel/CT053 (LUMMICAR trials), and CT103A (FUMANBA trials).

Ide-cel/ idecabtagene vicleucel update

Ide-cel is approved for patients with relapsed and refractory multiple myeloma who have received at least three previous lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and whose disease has progressed since receiving the last treatment. It was granted Conditional Marketing Authorisation from the European Commission in June 2021 with a validity throughout the European Union (EU) from 18th August 2021. The company manufacturing ide-cel (BMS/Celgene) is required to provide further evidence on the safety and efficacy of the drug as this evidence becomes available from ongoing clinical trials and, in particular, data on long-term safety is still expected. The phase 2 (KarMMa) clinical trial, which led to ide-cel's

approval, investigated the safety and efficacy of ide-cel in adult patients with relapsed or refractory multiple myeloma who had received at least three prior lines of therapy and continued to have worsening disease or no response to their last treatment. Out of the 140 patients enrolled, 94 responded to the treatment and remained in remission for approximately 11 months. Of the 140 participants, 42 had a complete response (their cancer was not detectable using conventional diagnostic methods) and 33 patients achieved a minimal residual disease (MRD) negative status (no cancer cells could be detected using advanced diagnostic techniques). A phase 3 study (KarMMA-3) is currently investigating ide-cel versus standard of care in triple-class-exposed patients with 2 to 4 prior lines of therapy.

Cilta-cel/ ciltacabtagene autoleucel updates

- **LocoMMotion:** In this trial, a Real World (RW) patient cohort was enrolled and treated with standard of care treatments that matched the CARTITUDE-1 cohort in terms of prognosis characteristics (refractory status, risk group, number and duration of prior lines, age and frailty). Researchers compared patients' progression free survival (PFS) and overall survival (OS) in these two cohorts. Patients treated with cilta-cel had better outcomes.
- **CARTITUDE 2:** Michel Delforge (Belgium) presented the results of the phase 2 clinical trial investigating cilta-cel in lenalidomide-refractory patients with progressive multiple myeloma after 1-3 prior lines of therapy (median = 2). Patients experienced early, deep and durable responses with an overall response rate of 95%, including 90% of the patients reaching very good partial response or better and 85% reaching complete response (out of 20 patients). No additional toxicity was reported (as compared to CARTITUDE-1 results). 19/20 patients experienced CRS which resolved within 7 days and 2/19 patients had a CRS grade >2. Given these preliminary results and the manageable safety profile, results of the ongoing follow-up will assess the impact of bringing cilta-cel to earlier lines of therapy. Kwee Yong (UK) added that CAR-T at frontline data is expected from ongoing trials and is a great promise as it will be followed by treatment-free intervals.
- **CARTITUDE-4:** the phase 3 study of cilta-cel versus standard triplet regimens in RRMM patients refractory to lenalidomide is ongoing.

PHE885

PHE885 is an autologous BCMA-directed CAR-T cell therapy which is currently in a phase 1 clinical trial. Preliminary data obtained from RRMM patients is encouraging. After a median follow-up of 3.5 months, 8/15 (53%) patients responded to the treatment. 2/15 (13%) experienced grade >2 CRS, 4 patients had grade 2 neurotoxicity related to PHE885 and no patients had severe ICANS. Longer follow-up and further analysis are required to confirm these results.

2.2. Other targets

MCARH109

A phase 1 trial for RRMM patients using GPRC5D targeted CAR-T cells is ongoing. GPRC5D is highly expressed in plasma cells, with a similar distribution to BCMA. This is an autologous GPRC5D CAR-T.

3. THE FUTURE OF CAR-T THERAPY

Gamma secretase inhibitors

Irreversible loss of the target antigen BCMA after relapse can happen following CAR-T therapy. Stanley Riddell (US) explained how the expression of BCMA on myeloma cells is regulated by gamma secretase. This enzyme can break down proteins like BCMA at the surface of the cells and its inhibition can increase BCMA expression 15 times. Therefore, to improve CAR-T therapy, they initiated a CAR-T clinical trial in 18 RRMM patients with or without the addition of a gamma secretase inhibitor (GSI). With GSI the frequency and the density of BCMA+ tumour cells increased. GSI was well tolerated in patients and CRS events were similar in both groups. Interestingly, 38,9% of patients had prior BCMA therapy. However, CAR-T + GSI induced a less durable response in these patients (PFS=2 months) while the others experienced a durable response (PFS not reached yet). This could mean that CAR-T resistance is not linked to BCMA expression itself and that further work is needed to answer the clinical needs of these patients.

Next generation CAR-T therapy

CAR-T therapy risks comprise antigen escape, immunosuppression, off-target toxicity and CRS. Several new approaches try to overcome these issues as well as reducing costs. Among them, Yvonne Chen explained that bispecific CAR-T cell therapy is giving promising results in a US phase 1 lymphoma clinical trial. Median progression free survival has not been reached and there is a high response rate at low dose, with no neurotoxicity and a maximum CRS grade of 1. In the Netherlands, Maria Themeli described their investigations on iPS-derived CAR-T cells, as they could provide unlimited off-the-shelf CAR-T products, and be given to multiple recipients, reducing costs. Induced pluripotent stem (iPS) cells are derived from skin or blood cells and reprogrammed to become stem cells which can give rise to all kind of cells. In this case, they can be used to generate T cells. There are still risks of rejection by the recipient and a lot of challenges in the field, but the first phase 1 iPS-derived CAR-T cell clinical trial is currently ongoing. Another approach is to change target. The current most advanced or approved CAR-T treatments target BCMA, a protein highly expressed on myeloma cells. Other molecules are expressed at high levels on myeloma cells and could make good targets, but many of these are also expressed on healthy cells, posing major risks of side effects due to attacks on non-tumoral tissue. Jort van der Schans (Netherlands) presented how dual CAR targeting could be a solution, using CD38

and CD138 targets, to only activate T cells in presence of cells which possess 2 tumour antigens, the myeloma cells, and not in healthy cell which might express one or the other tumour antigen. The current in vitro and in vivo results are promising.

Microbiome

Interestingly, the microbiome plays an important role in response to CAR-T treatment. Indeed, Christoph Stein-Thöringer (Germany) presented how antibiotic treatments given before therapy decrease patients' survival rate. They established a list of high-risk antibiotics that increase the incidence of disease progression after therapy, and identified microbial species that can modify the activity of T cells and CAR-T cells and predict disease progression in CAR-T patients.

Allogenic CAR-T

Allogenic CAR-T cells are generated from a healthy donor, while autologous CAR-T cells come from each patient undergoing CAR-T cell therapy. The main advantage of allogeneic CAR-T cells is the scaled-up industrialised process which makes batches immediately available for patients. Indeed, autologous CAR-T cells require complex logistics and manufacturing, as well as time between leukapheresis and CAR-T cell infusion. The clinical indications are the same and the risks and issues are mostly similar (CRS, issues related to gene modification and other side-effects). However, allogeneic CAR-T cells also present the risks of developing graft versus host disease, to reject the allogeneic cells, and toxicity related to intense lymphodepletion). Moreover, the persistence of the cells in patients is shorter with allogeneic CAR-T cells (weeks to months as compared to months to years with autologous CAR-T cells). During the meeting, clinical results of the Allo-715 product (UNIVERSAL trials) were presented. Only 5 days between enrolment and therapy were needed. The product was well tolerated among the 24 patients enrolled and there was no graft versus host disease issue. However, mild CRS events were reported and 3 patients died from infection complication.

4. UPDATES FROM WÜRZBURG (GERMANY)

Michael Hudecek gave an update on current myeloma work conducted at the University of Würzburg, Germany (UKW). They are currently working on the EU CARAMBA project which involves a CAR-T clinical trial targeting Slamf7, a protein highly expressed on malignant plasma cells. This phase I/IIa trial aims to assess the feasibility, the safety and the antitumour activity of the product. While cilta-cel and Abecma take the advantage of the viral machinery of a viral vector to enter into the cells and introduce the genetic material encoding the CAR, it is hoped that this new product will provide a clinical proof-of-concept for virus-free CAR gene transfer using the advanced Sleeping Beauty transposon technology. This virus-free method aims to increase safety and reduce the costs associated with CAR-T cell manufacturing. They are currently at the stage of testing the different escalating doses and already see a regression of serologic myeloma markers in enrolled patients, while they demonstrated that the manufacturing process

was efficient and stable. Further data will be needed to confirm these results. Another project is dedicated to enhancing the BCMA expression of myeloma cells, as BCMA is the target of many myeloma drugs. Indeed, studies showed the loss of BCMA after relapse in some CAR-T treated patients who also presented a lack of response to retreatment. At UKW, they are working on a BCMA CAR-T 2.0 together with trans retinoic acid (ATRA) treatment, which enhances BCMA expression on myeloma cells. UKW is also involved in the European IMI T2EVOLVE project, which aims to develop an innovation ecosystem that will accelerate the development of CAR-T therapies in the EU by bringing academic and industry stakeholders together. They are establishing good practice in CAR-T clinical trials and gold standards, which should increase trial reliability.

5. CAR-T ELIGIBILITY

What are the predictors of a poor response to CAR-T therapy? There are several factors that could be expected to lead to various responses: patient-related factors such as age, frailty and co-morbidities; disease-related factors such as refractory status, tumour burden, risk group, extramedullary disease and gene expression profile; treatment-related factors such as prior lines of therapy, bridging therapy and lymphodepleting chemotherapy, and other factors such as quality and quantity of leukapheresed cells.

Is there an age limit for CAR-T therapy? How fit should patients be? What about central nervous system involvement? Inger Nijhof explained that data from the KarMMa trial show that the efficacy and safety results were good in all subgroups and did not vary according to number of prior lines of therapy, or whether patients had undergone bridging therapy or not. Age had no impact and should not be a limiting criterion if other eligibility criteria such as fitness are met. Extramedullary disease had also no impact on outcomes. However, R-ISS III patients had a lower overall response rate and progression-free survival (PFS), as well as a shorter duration of response. Similarly, data from CARTITUDE-1 showed that efficacy was sustained in high-risk subgroups, but high-risk cytogenetic patients had a shorter PFS and overall survival.

How to choose between CAR-T therapies? Cilta-cel seems to lead to longer responses and lower neurotoxicity as compared to ide-cel (Abecma). However, if there is choice between the two products, patient characteristics, expected toxicity and availability (time frame, spots) need to be considered. Patient- and disease-related factors but also patient preferences need to be considered to choose the most effective regimen that is safe and maintains good quality of life.

6. CAR-T TOXICITY

6.1. Adverse effects

CRS

Claire Roddie explained that Cytokine Release Syndrome (CRS) affects 30% to 100% of all patients, with grades 3-4 reported in 10%-30% of the patients. Its incidence depends on the CAR-T product, the disease characteristics and the CRS grading system used. It occurs 1 to 14 days post-infusion, and lasts for 1 to 10 days. Rare, delayed cases have been reported. CRS is characterised by a fever $\geq 38^{\circ}\text{C}$, haemodynamic instability (which includes symptoms like abnormal or unstable blood pressure, abnormal heart rate, restlessness and shortness of breath) and hypoxemia (below-normal blood oxygen level). Several factors increase the risk of high-grade CRS, including tumour burden, infection, CAR-T dose and CAR-T product. CRS is usually treated with tocilizumab and eventually dexamethasone. Methylprednisolone can be used for grade 4 CRS and alternative treatments include siltuximab and anakinra, although limited clinical data is available.

ICANS

Immune effector cell-associated neurotoxicity syndrome (ICANS), or CAR-T associated neurotoxicity, is a clinical and neuropsychiatric syndrome that can occur within days or weeks post CAR-T infusion. Symptoms are variable and can include confusion, delirium, somnolence, memory impairment, attention, orientation or language issues, and vision changes. ICANS could be due to disruption of the blood-brain barrier and the activation of microglia (the immune cells of the central nervous system) lead by pro-inflammatory cytokines. The risks of developing ICANS depend on the CAR-T products, increases with the dose and the disease burden. ICANS occur more often in patients with pre-existing neurological conditions, and/or experiencing early, severe CRS. High fever ($\geq 38.9^{\circ}\text{C}$) and haemodynamic instability within 36 hours post CAR-T infusion is a predictor of severe ICANS. ICANS resolves spontaneously in most people, but occasional cases are fatal. Most cases of ICANS reported after anti-BCMA CAR-T therapy have been mild and transient. Early recognition and management are critical and rapid involvement of neurology and ICU teams is recommended. ICANS is managed with supportive care (grade 1) and corticosteroids ($>$ grade 1) which do not affect CAR-T efficacy although long-term exposure can be associated with shorter PFS. When grade 1 CRS is concomitant to grade $>$ 1 ICANS, steroids will be given (and tocilizumab for higher CRS grades). Alternative agents include siltuximab and anakinra but clinical data for its use in ICANS management is limited.

MAS

Macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis (HLS) is suspected when a patient has a persistent fever despite CRS management. Other symptoms include prolonged cytopenia,

liver dysfunction and blood coagulation issues. MAS can be treated with dexamethasone and anakinra and eventually methylprednisolone. In refractory CRS/MAS cases, chemotherapy can be used but available data is not sufficient and there is a risk of ablating the CAR-T cells.

Cytopenia and infections

Max Topp (Germany) explained that cytopenia (a decrease of the number of mature blood cells which can lead to shortness of breath, frequent infections, and fatigue) is more common in CAR-T patients and that its severity correlates with CRS grading. Other risk factors are prior infections and the use of steroids. Most infections occur during the first 30 days after infusion and differ between CAR-T product recipients. To prevent infections, he recommends giving prophylaxis for bacterial, viral and fungal infection to all CAR-T patients. As infection complications are more common with prolonged cytopenia and severe CRS grades for which patients receive high doses of steroids, adjusting prophylaxis for these patients is also recommended.

Cardiac toxicity

Daniel Chen (UK) talked about cardiac toxicity. He believes that CRS is the stronger predictor of cardiac complication (CRS grade 2 or higher), together with pre-existing cardiac disease and high tumour burden. However, he thinks that patients who have pre-existing cardiac conditions should not be excluded from CAR-T therapy, but carefully monitored prior to and after therapy, to detect and manage efficiently any cardiac complications.

Pharmacology

Carl June (US) reported that the pharmacology of CAR-T products is very different from classical drugs. Indeed, CAR-T is a process, not an inert drug, and CAR-T cells which deliver effects might evolve in patients over time. The cells causing efficacy or toxicity might not be the same as the one infused. Autologous T cells are inherently safe and can persist for a decade in patients (the first leukaemia CAR-T treated patients have just reached 10 years remission), while allogenic T cells (coming from cord blood, healthy donors or iPS cells) need further investigation.

Safety measures

In general, CAR-T safety is ensured by regular critical reviews of efficacy, safety and clinical outcomes at local and central levels. The European Group for Blood and Marrow Transplantation (EBMT) recommends that CAR-T is delivered through centres accredited for hematopoietic cell transplantation. The EBMT registry is now registering and monitoring European CAR-T recipients as well and, together with the European Haematology Association (EHA), they established the GoCART consortium to harmonise standards, guidelines and regulatory requirements across the EU and they will publish their recommendations.

6.2. Safety of commercial products

Ide-cel

The phase 2 KarMMa trial showed that 84% of patients experienced CRS (6% >grade 2) and that 18% suffered from neurotoxicity (4% = grade 3). Other reported adverse events were neutropenia, anaemia, thrombocytopenia, leukopenia, lymphopenia and infections. Ide-cel is approved in the EU for patients with RRMM who have received at least three previous lines of therapy, including an IMiD, a PI, and an anti-CD38 antibody, and whose disease has progressed since receiving the last treatment.

Cilta-cel

CRS was reported in 95% of the patients (92 patients), with a median time to CRS onset of 7 days and a median duration of 4 days. 95% of the cases were grade 1-2. Neurotoxicity was observed in 21% of the patients (10% >grade 2). Other reported adverse events include neutropenia, anaemia and thrombocytopenia. The US Food and Drug Administration (FDA) approved cilta-cel, marketed as Carvykti, in February 2022. It is specifically approved for the treatment of patients with relapsed or refractory myeloma after four or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. Decision from the European Medicines Agency (EMA) is expected later this year for cilta-cel approval in EU.

7. CAR-T ACCESS

Nathalie Asherie (Israel) shared her experience with locally produced CAR-T cells. With limited financial and human resource, they managed to develop a non-commercial, second generation novel BCMA CAR-T product. They demonstrated the antitumoral effect in vitro, in vivo, ex vivo and are now enrolling patients in a phase 1 clinical trial. This could be a major hope for countries where commercial products will encounter difficulties in reaching the market, and should encourage more academic CAR-T clinical trials in Europe.

The cost for the in-house production of these BCMA CAR-T cells is around US\$10,000 per patient. This does not include manpower, maintenance of the cellular therapy unit (environmental testing, cleaning, GMP-grade cleaning reagents, etc.). Indeed, to release a drug product for cellular therapy, a GMP accreditation is required. According to the European Medicines Agency (EMA): "Good manufacturing practice (GMP) describes the minimum standard that a medicines manufacturer must meet in their production processes. Any manufacturer of medicines intended for the EU market, no matter where in the world it is located, must comply with GMP." This ensures high quality of the medicine, and appropriateness for the intended use and that it meets the requirements of the marketing authorisation or clinical trial authorisation. With these additional expenses, the total production cost could reach around \$25,000 per patient, without hospitalisation fees and additional medical tourism fees, which are also not included in the cost of commercial CAR-T therapy. Of note,

ide-cel (Abecma) is currently listed at \$419,500 per dose in the US.

8. COVID-19 AND CAR-T THERAPY

Arnon Nagler (Israel) described the consequences of the COVID-19 pandemic on CAR-T therapy. Because of the high mortality rate of cancer patients after SARS-Cov-2 infection and because they might be waiting for CAR-T therapy without any other therapeutic choice, it is important to ensure therapy continuity. However, several factors affected the delivery of CAR-T cell therapies during the pandemic: disruption of healthcare and overwhelmed health workers, issues in the supply chain of commercial CAR-T cells, closing of borders which created shipping issues, difficult access to ICU and shortage of tocilizumab which is used in CRS management, and pauses in clinical trial enrolment during lockdowns. Nagler presented the results of a survey on the activity of European CAR-T centres in 2020 as compared to 2019, which showed that 29% of the centres delayed therapy, with 55% of patients delayed for 1 month, 26% for 1-6 months, and 16% who did not get therapy at all. In 68% of the cases, the delay required an additional therapy prior to CAR-T therapy. He thinks that the pandemic should not serve as a reason to delay CAR-T therapy as it is not a realistic option for patients in need. It seems that the virus cannot be transmitted through the infused product, but myeloma patients who contracted COVID-19 after CAR-T cell therapy had a poor outcome (with a 15 times higher mortality rate) and longer isolation should be considered. He recommends patients to be protected using all available measures (prevention, social distancing, masks, vaccination of healthcare professionals and family members, virtual outpatient visits, priority to products that can be given on an outpatient setting). Post-CAR-T vaccination is recommended after at least 6 months post infusion. Further work is required to determine the predictors of vaccine response, efficacy and safety in CAR-T recipients.

9. THE PATIENTS' SIDE

CAR-T, a patient's perspective

A French lymphoma patient treated at the Saint Louis Hospital (Paris) shared his journey from diagnosis to CAR-T therapy. One year after his treatment, he is now in remission. For him, the most difficult time was the period of uncertainty before his diagnosis. Then, at the time of his CAR-T treatment, he found it very important to understand the CAR-T process and that everything was done with transparency. He enjoyed getting an information booklet that was useful to answer his family and friends' questions, and at the hospital, he was also questioned to make sure he understood the process. This helped to reduce anxiety. He had a lot of trust in the team when the moment came to choose between transplant and CAR-T and is grateful to the care team for their medical and human work, and who were extremely well organised and co-ordinated despite the multidisciplinary aspect of the CAR-T treatment. He felt reassured to see that everyone, especially the nurses, knew his case and health status very well. For these reasons, he felt better at the hospital than at home between sessions, where he was more worried.

For him, it was therefore important to keep the contact with the medical team from home. After the treatment itself, he experienced strong fever but got very good care and attention at the hospital. His family was very loving, supporting and positive. He tried not to worry his kids about the disease. He did not have to take days off work and thought it was a good decision because his job kept him busy, and he would have missed great work projects otherwise. It was a positive experience!

Patient experience (Lymphoma Coalition)

Lorna Warnick (Canada), the CEO of the Lymphoma Coalition, presented the results of their Global Patient Survey. In particular, they investigated the patient-doctor relationship and 78% of the patients declared that their healthcare decisions are mostly influenced by their doctor, who is also their preferred source of information (before websites and patient organisations). Indeed, they understand them and trust what they say. Therefore, as the CAR-T therapy process requires the involvement of a multidisciplinary team, it is important that doctors introduce to patients the rest of the team and how valuable they are, as doctors cannot do everything. Honesty and transparency are key to keep patients sharing about their health issues, and this is only possible if the problems they report are taken seriously. As an example, 81% of patients experienced fatigue, but only 57% of their doctors followed up on this symptom. A lot of patients do not report depression, fear and anxiety issues and would like more information on support for self-care, psychological support, and support for their family. Half of them want more information on side-effects to become more confident in managing health problems on a daily basis. To conclude, Lorna Warnick recommends doctors create an environment of trust that includes the entire team of healthcare professionals involved, especially because this team is generally new for patients; to ask patients and their caregivers the right questions to ensure their needs are well addressed, to give understandable information according to patients' will, and to remember that patient organisations can help!

Patient and caregiver experience

Charlotte Stenson (UK) presented the results of the interviews of lymphoma patients prior to and after CAR-T infusion, as well as after 18 months. Patients have complex physical, functional and psychological unmet needs which are already there prior to therapy and which require personalised assessment and management. However, some patients experienced significant adverse events after discharge and felt under-prepared and under-supported during that period. The psychological burden was high due to prognostic uncertainty and could be better addressed with palliative care teams and psychology. It is important to work on management of expectation through effective communication on prognosis, but also by supporting hope. It also appeared that having a CAR-T nurse specialist was crucial to improving patients and their caregivers' experiences. Importantly, patients wanted to hear from other patients who had been through that journey, to access real-life information they could relate to, on top of the medical details. To conclude, developing a model of multidisciplinary supportive care seems essential!

Charity

Kristina Modic, the president of the Slovenian Lymphoma and Leukaemia Patient Association (a member of MPE) talked about their joined action with haematologists to organise a fundraising campaign with the aim to buy the state-of-the-art CAR-T equipment they needed to offer treatment options to many patients with blood cancer. The team, who had a very good operation strategy, used traditional and social medias to daily communicate about their campaign, got help from other blood cancer patient organisations, which offered to collect donations, organised 5 press conferences with the support of healthcare professionals and got the support of patients and their relatives. After only 7 weeks, they successfully raised €850,000 and bought two CliniMACS devices. These machines can process cells automatically and are used for CAR-T cell manufacturing. Kristina Modic and Prof Dr Samo Zver were awarded a European Citizen's prize in 2021 for their impactful action.

For those who would like to start their own charity campaign, Kristina Modic recommends having a clear purpose and the support of patients, patient advocates and healthcare professionals. It requires good co-operation with the medias and to use patients' stories and healthcare professionals' arguments, which are very important for a good communication with the public. Finally, transparency from the beginning to the end of the campaign is crucial for its success.

Patient communication

Maria Jose Kersten described how important patient communication is during the CAR-T process. It needs to be bidirectional: from the patient, to understand his/her personal situation, treatment goals, ongoing treatment and previous therapies, and from the healthcare team to inform about the CAR-T journey. The CAR-T co-ordinator is responsible for the communication about logistics, infusion and appointments, the haematologist for communicating about eligibility, treatment trajectory and side-effects, and the nurse specialist for additional information on side-effects, home monitoring (for the caregiver), discharge, and important contacts. Good communication is tailored to individual patients, as they have various levels of health literacy, prior knowledge and information needs. The information needs to be structured, repeated, simple and given with empathy. It can be supported by different kind of materials (written, videos, animations) and in stressful situations, one should avoid information overload. It is also crucial to develop educational materials in co-creation with patients and caregivers according to identified information gaps and needs and to run quality of life studies and report about it. To this aim, a T2EVOLVE and QUALITOP international survey will be launched to collect patients' CAR-T experiences and needs, and its impact on their quality of life, develop new patient friendly materials and ensure that this patient experience is included in HTA decisions on reimbursement.

GLOSSARY

- **Adverse event (AE) or side-effects:** any unfavourable event and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment or procedure; in the context of clinical trials, adverse events are given a specific grade in severity based on specific criteria:
 - Grade 1: mild
 - Grade 2: moderate
 - Grade 3: severe
 - Grade 4: life-threatening
 - Grade 5: death
- **Allogeneic CAR-T cells:** the T cells used to make CAR-T cells are generated from peripheral blood mononuclear cells from healthy donors, umbilical cord blood or derived from induced pluripotent stem cells (iPSCs)
- **Anaemia:** low levels of red blood cells in the body
- **Antibiotic treatment:** medication used to treat or prevent some types of bacterial infection
- **Antibodies:** proteins that the body creates to fight infection
- **Approval:** marketing authorisation given by the competent authorities (European Medicines Agency [EMA], in the European Union, Food and Drug Administration [FDA], in the USA)
- **Autologous CAR-T cells:** the original T cells used to make CAR-T cells come from the patient him/herself
- **Autologous stem cell transplant (ASCT):** a type of stem cell transplant where a patient's own stem cells are taken out of their body, processed, and reinfused after a patient receives chemotherapy with the goal to replace damaged cells
- **B cell maturation antigen (BCMA):** treatment target for multiple myeloma due to its highly selective expression in malignant plasma cells
- **Bispecific CAR-T cell therapy:** targeting two tumour antigens at once (instead of one for regular CAR-T), which is explored to increase long-term efficacy and reduce the risk of relapse
- **Chimeric antigen receptor (CAR T) cell therapy:** a type of immunotherapy treatment where T cells are genetically modified in a laboratory to make them find myeloma cells more easily. CAR-T cells are then infused in a patient, they bind to myeloma cells and stimulate the immune system to kill the cancer cells

- **Chemotherapy:** therapy which prevents myeloma cell division and replication and induces cell death
- **CD38 monoclonal antibodies:** they bind to the CD38 receptor, which is a protein found in high levels on myeloma cells. These monoclonal antibodies are used to help the immune system kill cancer cells. Examples: daratumumab (Darzalex) and isatuximab (Sarclisa)
- **Central nervous system (CNS):** the brain and the spinal cord
- **Complete response (CR):** a treatment response type where less than 5% of plasma cells can be found in the bone marrow and no paraproteins are detectable in blood or urine
- **Cytokine release syndrome (CRS):** a side-effect characterised as a systemic inflammatory response causing flu-like symptoms such as fever, body aches and fatigue, which in severe cases can be life-threatening
- **Cytokines:** proteins released by cells throughout the body to stimulate cell growth, killing target cells and microbes, which is part of the immune response
- **Cytopenia:** a decrease of the number of mature blood cells which can lead to shortness of breath, frequent infections, and fatigue
- **Enzyme:** protein that acts as biological catalyst (biocatalyst) which accelerate chemical reactions
- **European Union (EU):** political and economic union of 27 member states located in Europe
- **European Medicines Agency (EMA):** agency of the European Union in charge of the evaluation and supervision of medicinal products
- **Extramedullary disease or plasmacytoma:** a condition where cancerous myeloma plasma cells are found outside of the bone marrow, usually in the form of a tumour
- **Gamma secretase inhibitor (GSI):** drugs initially developed to treat Alzheimer's disease, now used as anticancer agents
- **Graft versus host disease:** a condition that can occur after transplants of bone marrow, stem cells, or other immune cells where the graft (cells from the donor) recognise the host (recipient of the transplant) as foreign and attack the recipient's body
- **Haemodynamic instability:** abnormal or unstable blood pressure, which can cause inadequate blood flow and advanced heart failure. Symptoms can include chest pain and abnormal heart rate
- **Health Technology Assessment (HTA):** evaluation of properties, effects, and/or impacts of healthcare technology which are assessed to inform decision-

making in the healthcare area

- **High-risk myeloma:** risk category which includes patient-specific factors such as old age, poor performance status and co-morbidities; clinical factors such as primary plasma cell leukaemia and extramedullary disease or plasmacytoma; disease-specific biological factors such as deletion 17p, t(4;14) and high-risk gene expression profiling signatures. High-risk myeloma is associated with lower life expectancy. The definition of high-risk myeloma is continuously evolving, following new scientific discoveries
- **Hypoxemia:** below-normal blood oxygen level
- **Immune effector cell-associated neurotoxicity syndrome (ICANS):** also known as CAR-T associated neurotoxicity which is a clinical and neuropsychiatric syndrome that can occur within days or weeks post CAR-T infusion. Symptoms are variable and can include confusion, delirium, somnolence, memory impairment, attention, orientation or language issues and vision changes
- **Immunomodulatory imide drugs (IMiDs):** drugs which prevent cell growth and blood supply formation to cells. Generate an anti-inflammatory response and stimulate an immune system response to kill cancer cells
- **Intensive care unit (ICU):** special department of a hospital providing intensive care medicine
- **In vitro studies:** studies or experiments done in a laboratory tube or dish, rather than in a human or animal (eg cell culture)
- **In vivo studies:** studies or experiments done on (or in) a living organism (laboratory animal or human)
- **Incidence:** measure of the probability of occurrence of a given condition in a population within a specified period of time
- **Induced pluripotent stem (iPS) cells:** cells derived from skin or blood cells and reprogrammed to become stem cells which can give rise to all kind of cells
- **Infusion:** when medication or fluids are administered in the veins through a needle or a catheter
- **Leukapheresis:** laboratory procedure on a blood sample during which white blood cells are separated out
- **Leukopenia:** low levels of leukocytes, a type of white blood cell which fights infections
- **Line of treatment:** the following are considered 1 line of treatment: a treatment of 1 or more cycle(s) of a single agent, 1 or more cycle(s) of a regimen consisting of a combination of drugs, a sequential therapy of various regimens (eg, several cycles of initial therapy followed by stem cell transplant, consolidation, and maintenance). When a treatment regimen is completely or partially changed

(unplanned addition or substitution of drugs), or when a new transplant is performed (even if the induction regimen is the same as for the first transplant), it is considered a new line of treatment

- **Lymphodepletion:** therapy given before a stem cell transplant, which is usually high-dose chemotherapy to kill remaining cancer cells and get rid of blood-producing cells that are left in the bone marrow
- **Lymphopenia:** low levels of lymphocytes, a type of white blood cell which fights infections
- **Macrophage activation syndrome (MAS)** or haemophagocytic lymphohistiocytosis (HLS) is suspected when a patient has a persistent fever despite CRS management. Other symptoms include prolonged cytopenia, liver dysfunction and blood coagulation issues
- **(myeloma) marker:** measurable indicator of the severity or the presence of myeloma
- **Mean:** average of data/numbers
- **Median:** middle value in a list of data/numbers
- **Microbiome:** community of microorganisms (symbiotic and pathogenic) that can be found in or on vertebrates (eg, in the gut). Bacteria, viruses, and fungi can be part of microbiomes
- **Microglia:** the immune cells of the central nervous system
- **Minimal residual disease (MRD):** use of specialised testing to test for microscopic levels of plasma cells in a patient who had a complete response to treatment
- **Monoclonal antibodies (mAb or moAb):** drugs which are antibodies engineered to mimic human antibodies and bind to specific targets on cancer cells to recruit the body's immune system to kill the cancer cells
- **Multiple Myeloma (MM):** type of cancer of the bone marrow that forms in plasma cells. Normal plasma cells help fight infections by producing antibodies that recognise and attack germs while myeloma cells accumulate in the bone marrow and crowd out healthy blood cells. Symptoms include bone pain, anaemia, kidney dysfunction, and infections
- **Neurotoxicity:** a side-effect of some myeloma treatments that is characterised by confusion, lethargy, inability to speak, tremor and in severe cases can progress to seizures and a coma
- **Neutropenia:** low levels of neutrophils, a type of white blood cell which fights infections

- **Off-the-shelf:** product which is available immediately and does not need to be specially made
- **Outcome:** a clinical outcome or result is a measurable change in health, function or quality of life that results from an intervention/treatment or care (eg survival, decrease of pain etc)
- **Overall response rate/objective response rate (ORR):** the percentage of patients with partial response or better
- **Overall survival (OS):** number of individuals in a group who are alive after a duration of time
- **Partial response (PR):** a treatment response type that shows a greater than 50% reduction in paraproteins in the blood
- **Plasma cell:** type of cell found in the bone marrow that produces antibodies
- **Plasmacytoma or extramedullary disease:** a condition where cancerous myeloma plasma cells are found outside of the bone marrow in the form of a tumour
- **Prognosis:** the likely course of a medical condition
- **Progression-free survival (PFS):** duration for which patients did not experience disease progression during or after treatment
- **Progressive disease (PD):** a treatment response type that shows an increase by 25% of urine or blood paraprotein levels
- **Prophylaxis:** treatment given or action taken to prevent a disease
- **Proteasome:** protein complex in the body which degrades and gets rid of damaged proteins
- **Proteasome inhibitors (PIs):** drugs which block proteasomes; this results in the build-up of proteins inside myeloma cells to toxic levels, causing cancer cells to die. Examples: bortezomib (Velcade), carfilzomib (Kyprolis), ixazomib (Ninlaro)
- **Real world (RW) studies:** studies done to understand how a treatment is used in everyday clinical practice, as compared to the very controlled environment of clinical trials
- **Refractory:** when the number of myeloma cells and paraproteins continues to increase despite someone receiving treatment
- **Relapse:** myeloma that initially responded to therapy but after some time, myeloma plasma cell levels continue to increase
- **Relapse/Refractory Multiple Myeloma (RRMM):** myeloma which becomes

non-responsive or progressive on therapy after a remission on prior therapy

- **Remission:** classified as partial (some cancer cells or symptoms are present but at lower levels) or complete (cancer cells or symptoms are undetectable)
- **Revised International Staging System (R-ISS):** tool to risk stratify newly diagnosed MM patients as presented here:
 - R-ISS-1: patients with ISS-1 (serum ≥ 2 -microglobulin level < 3.5 mg/L and serum albumin level ≥ 3.5 g/dL), no high-risk cytogenetic abnormalities in iFISH [such as del(17p) and/or t(4;14) and/or t(14;16)] and normal LDH levels (below the upper limit of normal)
 - R-ISS-3 patients with ISS-3 (serum ≥ 2 -microglobulin level > 5.5 mg/L) and either high-risk cytogenetic abnormalities in iFISH or elevated LDH levels
 - R-ISS-2 all the other possible combinations¹
- **Sleeping Beauty transposon technology:** gene therapy strategy using synthetic DNA transposon designed to introduce defined DNA sequences into the genome
- **Stable disease:** no worsening or improvement of myeloma after treatment; also, disease that has previously responded to therapy and paraproteins levels have not increased
- **Stringent complete response (sCR):** a treatment response type that shows no detectable presence of paraproteins in blood or urine; absence of abnormal myeloma plasma cells in the bone marrow
- **T cell:** a type of lymphocyte, which are important white blood cells crucial for the immune system
- **Thrombocytopenia:** low levels of platelets in the blood; platelets are used by the body to stop bleeding
- **Triple class refractory:** patients who have previously been treated with a combination of three drugs, such as an immunomodulatory drug, proteasome inhibitor, and a monoclonal antibody, and are no longer responding to therapy
- **Transplant ineligible:** patients not considered good candidates for a stem cell transplant because of factors such as age, health status, physical status, and cancer stage
- **Very good partial response (VGPR):** a treatment response type that shows a greater than 90% decrease in paraproteins in blood and a paraprotein level in urine of < 100 mg/24 h
- **Viral vector:** molecular tool often used to deliver genetic material into cells

¹ Kastritis E. et al. Haematologica. Evaluation of the Revised International Staging System in an independent cohort of unselected patients with multiple myeloma. 2017 Mar;102(3):593-599. DOI: 10.3324/haematol.2016.145078 Epub 2016 Oct 27.



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