EBMT Satellite Symposium supported by Miltenyi Biotec

Exploit the benefits of cell therapy

45th Annual Meeting of the EBMT
Frankfurt, Germany

Sunday, March 24, 2019
12:30 p.m.–02:00 p.m.
Room: Harmonie A+B+C

EBMT
European Society
for Blood and Marrow Transplantation

AGENDA

12:30 p.m. **Welcome**
Peter Bader, Frankfurt, Germany

12:40 p.m. **Towards personalized transplantation care and a low-GVHD allogeneic hematopoietic stem cell transplantation platform with α/β TCR depletion and drug monitoring**
Jürgen Kuball, Utrecht, the Netherlands

01:00 p.m. **NK cell immunotherapy against AML and MDS – can outcomes be further improved by modulation of homing?**
Mattias Carlsten, Stockholm, Sweden

01:20 p.m. **Cell therapy platform to enhance outcome of high-risk leukemia – from graft engineering to lymphocyte engineering**
Michael Maschan, Moscow, Russian Federation

01:40 p.m. **Academic CAR T cells for national multicenter clinical trials**
Alvaro Urbano-Ispizua, Barcelona, Spain

CHAIR

Peter Bader, M.D., is Professor of Pediatrics at the Johann Wolfgang Goethe University in Frankfurt a. M., Germany. He received his medical degree from the Eberhard-Karls-University in Tübingen. Since October 2004, he is Head of the Division for Stem Cell Transplantation and Immunology and Vice Director of the University Children's Hospital in Frankfurt a. M., Germany.

Prof. Bader's research is focused in particular on pre-emptive strategies to prevent relapse after allogeneic stem cell transplantation in children and adolescence with malignant diseases. His group has built up a large transplant program focusing on T cell–depleted transplants using different donors, especially HLA non-identical relatives after reduced intensity conditioning. The development of post-transplant cell therapies, using tumor and leukemia peptide specific T cells, NK cells, and cytokine induced killer cells (CIK), as well as CAR T cell therapies, are important parts of Prof. Bader's research activities. An additional research topic is the characterization and application of mesenchymal stem cells for treatment of graft-versus-host disease (GVHD) and induction of immune tolerance to improve engraftment.

From 2008–2015, Prof. Bader was chairman of the Stem Cell Transplantation Committee of the International BFM Group. He has been elected as secretary of the German Society for Blood and Marrow Transplantation in 2012. From 2014–2018, Prof. Bader was chairman of the Pediatric Diseases Working Party (PDWP) of the European Group for Blood and Marrow Transplantation (EBMT).

Prof. Dr. Jürgen Kuball received his medical degree as hematologist at the University of Mainz, Germany, and was further trained at the Fred Hutchinson Cancer Center in Seattle, WA, USA. In 2007, he joined the Department of Hematology at the University Medical Center (UMC) in Utrecht, the Netherlands, as hematologist and immunologist. Prof. Kuball chairs the section Applied & Tumor-Immunology within the Laboratory of Translational Immunology and is scientific advisor of the UMC Utrecht spin-off company GADETA. Since 2013, Prof. Kuball chairs the Department of Hematology at the UMC Utrecht Cancer Center.

Towards personalized transplantation care and a low-GVHD allogeneic hematopoietic stem cell transplantation platform with α/β TCR depletion and drug monitoring

Jürgen Kuball

A stringent *in vivo* and *ex vivo* T cell depletion has since long time been known as an effective strategy to prevent severe GVHD[1]. E.g., Pasquini *et al.* have shown that CD34 selection of peripheral derived blood stem cells (PBSCs) of HLA-matched sibling donors results in a well-defined allograft with 0.01–1×10^5 TCRα/β$^+$ T cells/kg, resulting in a low incidence of acute GVHD as well as good leukemia control[2]. Subsequently, CD3 and α/β$^+$ TCR depletion entered clinical practice in haplo-SCT, matched related and unrelated donors[3–7]. These depletion techniques restrict TCRα/β$^+$ T cells to be around 0.1–1×10^5 TCRα/β$^+$ T cells/kg (comparable to CD34 selection) while preserving NK and TCRγ/δ$^+$ T cells[4], both potent immune subsets to control leukemia and infections[8]. TCRα/β$^+$ T cell depletion resulted in a low incidence of acute GVHD in a cohort of patients with both malignant and non-malignant diseases[4–7]. However, still many variations in terms of immune reconstitution can be observed within the context of TCRα/β$^+$ T cell depletion, which cannot be solely explained by graft compositions. Other factors, which interfere with immune reconstitution, might be derived from drugs used during the conditioning of a patient. A first step to overcome inter-individual variants is the administration of busulfan based on dose levels[9], which has been shown to reduce toxicity. In addition, inter-individual variations in active ATG levels have been acknowledged to impact immune reconstitution and clinical outcomes[10]. Within this context we will discuss the impact of ATG as well as additional drugs such as fludarabine[11] in regard to TCRα/β$^+$ T cell depletion in order to reduce inter individual variations and improve immune reconstitution in all patients and thereby optimize clinical outcomes.

References
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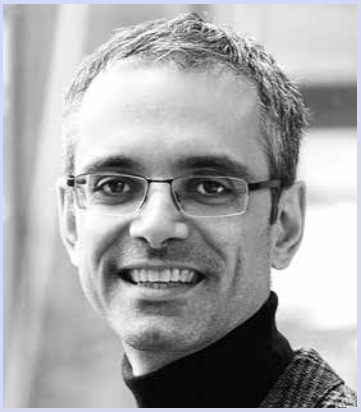
11. Langenhorst, J. B. *et al.* (2018) Clin. Pharmacokinet.: Epub ahead of print, Oct. 17.

Dr. Mattias Carlsten received his M.D. and Ph.D. from Karolinska Institute, Sweden, and has worked as a post-doc and staff scientist at the Hematology Branch, National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), USA. Now, he leads a research group at Karolinska Institute, while working as a physician at Hematology Center Karolinska, Karolinska University Hospital, Sweden. His research focuses on NK cell biology and utilization of NK cells for cancer immunotherapy with a particular focus on translating new findings from the bench to the bedside. Dr. Carlsten has experience from running clinical trials on adoptive NK cell transfer at both the Karolinska University Hospital and the NIH. He has been involved in multiple clinical studies of drugs aimed at bolstering tumor cytotoxicity by endogenous NK cell.

NK cell immunotherapy against AML and MDS – can outcomes be further improved by modulation of homing?

Mattias Carlsten

Natural killer (NK) cells are immune cells that in contrast to T cells can kill tumor cells without prior priming. The potential of using NK cells to treat patients with cancer was highlighted 17 years ago in a study where donor NK cells were shown to prevent leukemia relapse after allogeneic hematopoietic stem cell transplantation (HSCT). This study triggered a series of clinical trials on adoptive NK cell infusion to treat patients with cancer. Today we know that clinical protocols involving adoptive NK cell infusions can generate complete remissions (CRs) in patients with chemotherapy-refractory and/or relapsed acute myeloid leukemia (AML). We recently also showed that this approach prompts CR in patients with high-risk MDS and that the approach can be used to bridge patients with refractory leukemia to a potential curable allogeneic HSCT. Yet, regardless of study design, NK cell source and preparation, as well as whether post-infusion cytokine support is used or not, response rates in the large collection of small early phase clinical trials published today rarely reaches more than 30–50% in this poor prognosis patient population. This means to improve the efficacy of NK cell-based cancer immunotherapies, such as the use of CAR, checkpoint inhibition, and bi- and tri-specific antibodies are intensively being investigated. Studies now also start to address the potential of programming NK cells to selectively home to bone marrow (BM) compartments with the purpose of triggering more prominent anti-leukemia responses. In line with this hypothesis, we observed in our recent clinical trial that patients receiving NK cell grafts with expressed higher levels of CXCR4 had a higher probability of achieving a CR than those receiving NK cells with a lower level of CXCR4 cell surface expression. In this presentation, I will discuss the current results from adoptive NK cell therapies against myeloid leukemia. I will also provide examples on new methodologies to increase the propensity of infused NK cells to BM compartments as a way to improve their efficacy per se, but also to bolster the above-mentioned complementary approaches that all aim at enhancing the tumor targeting capacity of the NK cells once they have reached the malignant cells.



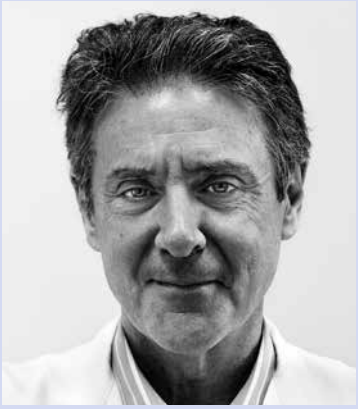
Michael Maschan, M.D., Ph.D., is the Scientific Director of the Hematopoietic Stem Cell Transplantation Department of the Dmitry Rogachev National Medical Center for Pediatric Hematology, Oncology, and Immunology in Moscow, Russia. He received his training in pediatrics and pediatric hematology at the Russian State Medical University. In 2011, he was awarded a doctoral degree for his thesis on histiocytic proliferative disorders in children. He is a member of the Histiocyte Society, the EBMT, and the American Society of Hematology. Currently, his transplant-related research is focused on the clinical study of graft manipulation in pediatric hematopoietic stem cell transplantation (HSCT), novel therapeutic approaches to leukemia control after transplantation, and cancer therapy based on gene-modified T cells.

Cell therapy platform to enhance outcome of high-risk leukemia – from graft engineering to lymphocyte engineering

Michael Maschan

Graft-versus-host disease (GVHD) remains the major obstacle to the success of HSCT. The negative impact of GVHD increases significantly with less compatible grafts, derived from matched unrelated donors (MUD) and haploidentical donors. Profound *ex vivo* T cell depletion of the graft was developed as the most reliable method of GVHD prevention, but this approach also holds significant risks, of which poor engraft-ment and severe infections are the most notable ones. Since 2012, our group used TCRα/β^+ T cell and CD19 depletion as a principal GVHD prophylaxis method in haploidentical and MUD transplantation. By the moment of this report, more than 600 transplantations were performed in pediatric patients suffering from malignant and non-malignant diseases. We were able to show that outcomes of HSCT from haploidentical related donors are not different and, under certain circumstances, may even exceed the results of HSCT from unrelated donors.

Refinement of the pharmacological component of the GVHD prophylaxis resulted in a steady improvement of GVHD control, with a 10% cumulative incidence of clinically significant GVHD. Further improvement of the platform was based on the use of donor-derived memory T cells (CD45RA–depleted) in an attempt to boost the recovery of pathogen-specific immunity. We have shown that use of low-dose memory DLI is safe after engraftment and may provide functional virus-specific immune responses. Based on this pilot trial we initiated a protocol of co-infusion of low-dose memory DLI with the graft. The preliminary analysis suggests that this approach improves early pathogen-specific immune reconstitution and is associated with a consistently low TRM of <3%. Further improvement of the outcomes of HSCT in high-risk leukemia is expected to be driven by systematic application of the new generation of cell-based therapeutics, including genetically-engineered CAR T cells, either as part of the transplantation platform, or as a standalone therapy.



Alvaro Urbano-Ispizua, Ph.D., graduated in 1982 at the Basque Country University, Bilbao, Spain and was trained in hematology in the Postgraduate School of Hematology of Hospital Clinic of Barcelona (HCP). From 1989–1990, he stayed at the Institute of Cancer Research of the University of London, analyzing the role of RAS mutations and BCR/ABL oncogene in hematological diseases. For 14 years, he was the head of the Research Unit of Cell Therapy and Stem Cell Transplantation at the HCP, one of the pioneers of BMT in Europe. In 2007, he moved to the University of Sevilla to lead the Department of Hematology of Hospital Virgen del Rocío. Dr. Urbano-Ispizua is currently Director of the Institute of Hematology and Oncology of Hospital Clinic of Barcelona and Full Professor of Medicine at the University of Barcelona. He is author or co-author of more than 150 articles. He has been the general secretary of the European Bone Marrow Transplant Group (EBMT) from 1998–2004 and the President of JACIE until October 2006.

Academic CAR T cells for national multicenter clinical trials

Alvaro Urbano-Ispizua

The use of chimeric antigen receptor T cells (CAR Ts) has shown outstanding efficacy in patients with relapsed/refractory (R/R) B cell lymphoid malignancies with responses rates of 80–90% in R/R acute lymphoblastic leukemia. Furthermore, it has shown stable complete remissions of 40% in R/R non-Hodgkin lymphoma and high overall responses rates (approx. 80%) in multiple myeloma patients and more recently in Hodgkin lymphoma patients (> 50). The efficacy of these CAR Ts was first observed in academic clinical trials in the USA and in China. The encouraging results of these CAR Ts have been confirmed in pharma sponsored clinical trials in large cohorts of patients in multicenter international sites. Based on these experiences, two CAR T products targeting CD19 have been approved by the FDA and the EMA and will be available in many European centers soon. It is expected that CAR Ts targeting BCMA for multiple myeloma will be the next. Other CAR Ts might follow soon like, e.g., CAR Ts directed against CD30.

The production of CAR Ts for European patients in both clinical trials promoted by the pharma industry and marketed CAR Ts are planned in a similar manner: after lymph apheresis of the patient at the point of care, cells are transferred to a centralized European facility in which lymphocytes are tested, frozen, and sent to a local site in the USA for individualized manufacturing of the CAR Ts.

The final product is tested for sterility and for assuring that it meets strict quality standards. From this centralized site, approved CAR Ts are released and delivered to the European point of care after travelling through the ocean. It is expected that, thousands of CAR Ts targeting CD19 will be prepared in an individualized procedure in each factory annually. This number will exponentially increase if CAR Ts against BCMA, CD30, or hopefully against other targets present in solid tumors are eventually incorporated to the CAR T catalog. The individualized production of the CAR Ts in a centralized site has advantages but also raises concerns. First, the core business of pharma companies has been to prepare and distribute a drug, not a sophisticated cell product from an individual patient for many years. There is no doubt that pharma companies will do a superb work but it is a reality that they are not familiar with handling cells from the bed site of the patient around the world. Second, centralization favors the efficiency of the process but it may also mean saturation and delays associated with peaks of high demands. Centralization may also be good for harmonization of standards of quality and sterility, but in case of contamination it might mean a transient stop of the production if there is no back up. Third, in this huge production of cells from different individuals, the possibility of crossing the products of two patients exists.

An alternative to the centralized manufacturing is the production at the point of care. This is feasible now, since there are automated, standardized, and consistent methods to prepare CAR Ts at an academic institution at a relative low cost and relatively easy for centers that are familiar with clinical trials involving cell therapy. In this symposium, I will present a proposal of an academic clinical trial in which the production of the genetic construct and lentiviral particles is centralized at the Hospital Clinic of Barcelona which will be distributed to other Spanish institutions for manufacturing the CAR Ts at the point of care.

Notes

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