Prevention and treatment of relapses after haploidentical HSCT

An ideal opportunity for cell-based therapy?

Chair:
Dr. Stefan Ciurea (MD Anderson Cancer Center, Houston, USA)
Kiadis Pharma company profile

Kiadis Pharma is a clinical stage biopharmaceutical company focused on research, development and future commercialisation of innovative cell-based immunotherapy products that provide for a safer and more efficacious treatment of blood cancers and inherited blood disorders, improving survival and quality of life and addressing significant unmet medical needs.

The Company believes that its products address current risks and limitations of allogeneic hematopoietic stem cell transplantation (HSCT). HSCT is considered the most effective curative approach to blood cancers and certain inherited blood disorders and Kiadis Pharma expects that HSCT will become a treatment option for many more patients once current risks and limitations are addressed.

ATIR™ (Allodepleted T-cell ImmunotheRapeutic) is an innovative cell-based therapeutic that addresses the key risks and limitations of current HSCT treatments in blood cancers and inherited blood disorders, being opportunistic infections, graft-versus-host-disease (GVHD), cancer relapse and limited donor availability.

Using Kiadis Pharma’s Theralux platform, T-cells that attack the patient, causing GVHD, are eliminated. At the same time, the full immune repertoire of donor immune cells, including immunological memory, is retained in the final product to fight infections. ATIR101 also contains T-cells from the donor that could eliminate residual cancer cells reducing the risk of return of the disease, which is called the Graft-versus-Leukaemia (GVL) effect. After an HSCT treatment, patients are highly susceptible and vulnerable to infections. Immune cells in ATIR™ will help fight these opportunistic infections and bridge the time until the immune system has fully re-grown from the stem cells in the transplanted graft.

ATIR™ products (see development status below) are cellular products for infusion which consist of donor lymphocytes (immune cells) specifically manufactured for each individual patient from a healthy, haploidentical family member’s donation.

<table>
<thead>
<tr>
<th>Products</th>
<th>Claim / Indication</th>
<th>Phase I</th>
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<tbody>
<tr>
<td>ATIR101</td>
<td>Providing T-cell based immune-protection reducing relapse rates and death from infections after HSCT in blood cancer patients</td>
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<td>ATIR201</td>
<td>Providing T-cell based immune-protection after curative-intent HSCT in Thalassemia patients</td>
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- Current status
- H2 2016 (Expected)
<table>
<thead>
<tr>
<th>Time</th>
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<tr>
<td>11:00</td>
<td>Welcome and general introduction</td>
<td>Dr. Stefan Ciurea</td>
<td>MD Anderson Cancer Center, Houston, USA</td>
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<td>11:05</td>
<td>Separating Graft versus Leukemia activity (GVL) from Graft versus Host Disease (GVHD) in transplantation</td>
<td>Prof. Arnon Nagler</td>
<td>Chaim Sheba Medical Center, Tel-Hashomer, Israel</td>
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<td>11:25</td>
<td>Donor lymphocyte infusion post HSCT: Risks versus benefits</td>
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<td>11:25</td>
<td>Use of unmanipulated DLI’s after haploidentical HSCT</td>
<td>Prof. Andrea Bacigalupo</td>
<td>Università Cattolica Policlinico Gemelli, Rome, Italy</td>
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<td>11:45</td>
<td>Use of manipulated DLI’s: engineered or photodepleted lymphocytes</td>
<td>Prof. Dr. Stephan Mielke</td>
<td>Universitätsklinikum Würzburg, Würzburg, Germany</td>
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<td>12:05</td>
<td>NK cells and CAR-T cells therapy to prevent disease relapse: What have we learned so far?</td>
<td>Dr. Stefan Ciurea</td>
<td>MD Anderson Cancer Center, Houston, USA</td>
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<td>12:25</td>
<td>Discussion / Questions</td>
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Dr. Stefan Ciurea is Associate Professor at the University of Texas, MD Anderson Cancer Center, Houston, Texas. He completed his training in Internal Medicine at Harrisburg Hospital at Pennsylvania State University, where he also served as Chief Medical Resident, followed by a 3-year Clinical Fellowship in Hematology-Oncology at the University of Illinois in Chicago. Here, he had the privilege to work in Prof. Dr. Ronald Hoffman’s laboratory, focusing on biology of myelofibrosis. Subsequently, Dr. Ciurea became interested in hematopoietic stem cell transplantation and was accepted for a year of Clinical Fellowship training in Hematopoietic Stem Cell Transplantation at the University of Texas, MD Anderson Cancer Center, Houston, Texas working directly with Prof. Dr. Richard Champlin. After completing his fellowship he joined the faculty in this department in 2008 as Assistant Professor and was promoted to Associate Professor in 2014.

Dr. Ciurea’s research interests are primarily focused on clinical-experimental and translational hematopoietic stem cell transplantation in the area of alternative donors. He developed a Haploidentical Transplant Program at the University of Texas MD Anderson Cancer Center, considering haploidentical transplants as a cost effective form of transplant that can be applied to almost every patient in need, regardless of race and unrelated donor availability.

Professor Arnon Nagler, MD, MSc, is Professor of Medicine at the Tel Aviv University, Israel, and visiting Professor at the Pierre and Marie Curie University, Paris, France. He received his medical training at the Hebrew University-Hadassah Medical School, Israel; and then carried out a Postdoctoral research fellowship in hematology and bone marrow transplantation at “Stanford University Hospital” Palo Alto, CA, in the USA, from 1986 to 1990. Dr. Nagler is one of the pioneers of the non-myeloablative and reduced intensity/toxicity allogeneic transplantations for both malignant and non-malignant disorders (Blood 1998). He established the first public cord blood bank and performed the first cord blood transplantation in Israel.

Dr. Nagler is Chair of the Acute Leukemia Working Party (ALWP) of the European Society of Bone Marrow Transplantation (EBMT), Director of the Division of Hematology, Chaim Sheba Medical Center, Israel, Director of Bone Marrow transplantation and Cord Blood Bank, Chaim Sheba Medical Center, Israel. He also serves on the Board of Directors of Netcord organization of cord blood banks and was the Netcord Treasurer from 2010-2013. Dr. Nagler has received several awards including the best scientific abstract award of the ASBMT/CIBMTR Tandem meeting (2004) and the best clinical abstract award of the NMDP Council Meeting (2004). In addition, Dr Nagler is a popular speaker and has made numerous, invited, international presentations and many oral presentations on almost annual basis in all international transplantation and hematology meetings - ASH,ASBMT/CIBMTR, EBMT, EHA, Exp Hematology (including a presentation at the presidential symposium) and invited presentation at the Gordon conference (Boston USA).
Dr. Stephan Mielke graduated and received his doctoral degree in 1999 from Georg-August University Medical School in Göttingen, Germany. He started his residency and fellowship program at the Department of Internal Medicine I at the Albert Ludwig University of Freiburg in Germany. Having been awarded a postdoctoral grant from the Dr.-Mildred-Scheel-Stiftung he worked in the Allotransplantation Section of the Hematology Branch at the National Institutes of Health, Bethesda, MD, USA from 2004 to 2007. Afterwards he joined the Department of Internal Medicine II at the Julius-Maximilian University of Würzburg in Germany where he carries responsibilities as attending internist since 2008. As a specialist for Hematology and Oncology he clinically focuses on allogeneic hematopoietic stem cell transplantation from matched and mismatched donors and on solid tumor therapy. He wrote a professorial thesis about selective T cell depletion strategies in allogeneic stem cell transplantation and received his habilitation in 2009. In 2011 he became director of the Adult Allogeneic Stem Cell Transplant Program and headed the successful JACIE-based accreditation process in 2013. In 2014 Dr. Mielke was announced professor at the Medical Faculty of the University of Würzburg. Dr. Mielke has a strong research interest in tumor immunotherapy and has been serving as a principal investigator on several clinical trials investigating the role of advanced cellular therapy particularly in the field of haploidentical transplantation. He has published 60 peer-reviewed articles with a cumulative impact factor of 330 and his papers received more than 2000 citations.

Dr. Andrea Bacigalupo has been the Head of the Division of Hematology and Stem Cell Transplants, at Ospedale San Martino, Genova, Italy 1989-2014. He is currently Head of the Hematology Department and Transplant Unit at Policlinico Gemelli, Catholic University, in Rome. He has been involved in stem cell transplants since 1976 and in the European Group for Blood and Marrow Transplants (EBMT) since 1977. He has conducted several prospective clinical trials in patients with aplastic anemia and in patients undergoing allogeneic transplants; in particular he has been the principal investigator of 9 prospective randomized studies in the field of GvHD. His main interests are bone marrow failure, GvHD and related complications, and graft versus leukemia reactions. He has also been interested in CMV and EBV infections, looking at early diagnosis and prospective studies on prophylaxis and pre-emptive therapy. Dr. Bacigalupo has served on the board of EBMT for many years, as EBMT secretary, chairperson of the Aplastic Anemia Working Party and then as president for the 1998-2002 term. He served as president of the Italian Group of Bone Marrow Transplantation (GITMO) for the 2002-2005 term. He has served on the Regimen Related Toxicity Working Group of the Center for International Blood and Marrow Transplant Research (CIBMTR). He has served on the Italian Council of the Ministry of Health for 3 terms (2001-2002, 2003-2005, 2007-2010). He is Associate Editor of the journal Bone Marrow Transplantation and Biology of Blood and Marrow Transplantation. He serves on the Board of Haematologica and of the Journal of Clinical Oncology. Dr. Bacigalupo has published over 600 articles in peer-reviewed journals.
Allogeneic hematopoietic stem cell transplantation (alloSCT) is a very effective therapeutic modality with curative potential in patients with hematological malignancies. The therapeutic efficacy is mainly based on the alloreactive reaction of donor lymphocytes against leukemic or other tumoral cells of the recipient named as ‘graft-versus-leukemia’ (GVL) or ‘graft-versus-tumor’ (GVT) effect. However, besides the beneficial GVL effect, the alloreactive reaction may attack normal tissues of the donor including skin, gut and liver that express up regulated levels of HLA molecules, and provoke the deleterious ‘graft-versus-host disease’ (GVHD). GVHD represents the major obstacle for successful alloSCT leading to substantial morbidity and mortality. Current trials have focused on a dual goal: augmentation of GVL and complete elimination of GVHD. From a theoretical point of view complete dissociation of GVL from GVHD can occur by selecting antigenic targets present on leukemic and malignant cells and absent from normal tissues. Hematopoietic tissue-restricted minor histocompatibility antigens and leukemia or tumor-associated antigens are ideal candidates for tumor-targeted immunotherapy. Other options for inducing anti-tumor immunity in the absence of GVHD are natural killer (NK) cell immunotherapy, amplification of immune responses by using monoclonal antibodies, tumor vaccination and bispecific T- and NK-cell engagers. Genetically modified immune effector cells such as T-cells armed with chimeric antigen receptors (CAR) or transduced with engineered T-cell receptors with anti-tumor specificity are another exciting emerging field of immunotherapy against malignancies.
Use of manipulated DLI’s after haploidentical HSCT

Prof. Andrea Bacigalupo (Università Cattolica Policlinico Gemelli, Rome, Italy)

Donor lymphocyte infusion (DLI) have been used now for over 25 years for the treatment of relapse after allogeneic stem cell transplants. DLI carry a significant risk of graft versus host disease (GvHD), which can be predicted by the dose of DLI, expressed as CD3+ cells/kg, and number of mismatched HLA antigens between donor and recipient. In several studies the feasibility and outcome of DLI from HLA haploidentical donors, for the treatment of relapse in Hodgkin’s disease, and acute leukemia was studied.

In patients with Hodgkin’s disease (HD) a total of 17 patients were treated with 56 DLI’s, following chemotherapy with Rituximab + Bendamustine. The dose of DLI ranged from 1x10⁵/kg to 5x10⁶/kg. Grade II GvHD occurred in 1 patient. Seven patients achieved a PET negative response (41%). Actuarial survival is 84% at 5 years. In patients with relapsed leukemia after a haploidentical BMT with post-transplant cyclophosphamide, 12 patients received induction chemotherapy followed by DLI (n=32) ranging from 1x10⁵/kg to 1x10⁷/kg. GvHD grade II-III occurred in 17% of patients. Actuarial survival at 1 year is 19%. In 20 patients with MRD + AML (based on WT1 expression), pre-emptive DLI’s were given, without chemotherapy. GvHD grade II-III occurred in 10% of patients; 96% of patients with a low MRD burden achieved MRD negativity and 29% relapsed despite DLI. Actuarial survival at 5 years is 74% in this population.

In conclusion, relapse of the original disease can be treated with DLI, following haploidentical transplants with PT-CY: the overall risk of developing grade II-III GvHD is 14%. Response rates depend on the underlying disease and its phase. Prophylactic DLI, would probably be more effective in reducing the risk of relapse.
Use of unmanipulated DLI’s: engineered or photodepleted lymphocytes

Prof. Dr. Stephan Mielke (University of Würzburg Medical Center, Würzburg, Germany)

Allogeneic hematopoietic stem cell transplantation provides a standard of care curative option for patients with a variety of hematological malignancies. For those having matched donors available, non-relapse mortality has reached a historical minimum. However, persistently high relapse rates and a lack of suitable donors for every patient in need remain as today’s obvious challenges. Selective depletion of host-reactive T cells causing GvHD may serve as a strategy to enhance graft-versus-leukemia effects in the presence of less or no immunosuppression thereby offering a curative option also to patients with high-risk malignancies. However, in cases where a matched donor is unavailable the use of alternative stem cell sources such as haploidentical family donors has harbored significant risks for the patients as the feasibility of this approach largely depended on sufficient in vivo and/or ex vivo T cell depletion strategies to ensure engraftment and avoid severe GvHD. Consequently infectious complications and relapse rates were increased, limiting the overall success of this approach. Therefore today’s optimized T cell depletion technologies aim to improve immune reconstitution by providing selected or manipulated lymphocytes for prophylaxis of infectious complications and relapse. In this context immunodepletion, suicide genes and photodynamic procedures have become the focus of today’s translational transplant approaches. Here, the experience with TH9402-based selective photodepletion and the use of prophylactic DLI’s (ATIR™) in clinical trials of haploidentical transplantation will be summarized and put into the broader context of alternative or complementary strategies.
NK cell and CAR-T cell therapy to prevent disease relapse: What have we learned so far?

Dr. Stefan Ciurea (MD Anderson Cancer Center, Houston, USA)

Different methods to control the alloreactivity in the haploidentical hematopoietic stem cell transplantation setting have made a major change in the way these transplants are performed. From T-cell depletion (using CD34+ selection) to a T-cell replete graft and post-transplantation cyclophosphamide, have demonstrated significantly better outcomes using a full graft and effective GVHD control post-transplant. Survival has more than doubled, and haploidentical transplants have now changed from a morbid, highly lethal procedure to a feasible type of transplant, with GVHD incidence and outcomes comparable with HLA matched transplants. While outcomes have improved primarily based on lowering the treatment-related mortality, the focus now lies on improving disease relapse post-transplant using cellular therapy, with the goal of enhancing anti-tumor effects of the allograft. Two unique approaches include the use of mbIL-21 ex vivo expanded NK cells for myeloid malignancies and CAR-T cells for B-cell lymphoid malignancies post-transplant.

The application of cellular therapy using NK cells and CAR-T cells after haploidentical transplant will be discussed. Focus will lie on the results of a phase I clinical trial using peripheral blood-derived NK cells expanded ex vivo for 14 days with K562 antigen presenting cells expressing membrane-bound IL-21 to prevent disease relapse after haploidentical transplants for patients with myeloid malignancies. Also early data concerning the administration of CAR-T cells generated using the Sleeping Beauty system after haploidentical transplants for B-cell acute lymphoblastic leukemia and non-Hodgkin’s lymphoma will be discussed. Preliminary results from these trials show potential to improve disease relapse in the absence of a higher incidence of acute GVHD.
SAVING LIVES WITH INNOVATIVE CELL-BASED THERAPY

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