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ABSTRACT

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WORKING PARTIES

WP001

Transplant indication for plasma cell disorders other than multiple myeloma

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Background: Small secretory B cell clones can cause severe diseases through the biologic activity of their monoclonal protein products. Because of their rareness and various clinical presentations, they are frequently overlooked by physicians.

Methods: The presence of any heart, kidney, liver abnormality; dysautonomic symptoms with hypotension, weight loss, peripheral neuropathy or signs of vasculitis should encourage the hematologist to initiate a careful evaluation. It is important to diagnose these diseases early, because appropriate treatment can prevent further or even reverse organ damage, improve quality of life, and even prolong survival in these patients.

Results: In this presentation, I will report the evidence of high-dose treatment for patients with light chain (AL) amyloidosis, light chain deposition disease (LCDD) and other monoclonal gammopathies with renal significance (MGRS) and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)

Conclusions: Finally, I will summarize transplant indication for these four rare disease entities.

Conflict of interest: Nothing to disclose.

WP002

Transplant indication for CML in 2018

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Background: CML is a myeloproliferative neoplasm characterized by the translocation t(9;22) also called Philadelphia chromosome, that represented, before the 2000's, one of the main indication for alloHSCT. Following the introduction of TKI in the early 2000's the use of alloHSCT for CML has dramatically decreased. Imatinib was the first TKI introduced and is mostly used as 1st treatment. In case of insufficient response, resistance or intolerance, CML patients can be treated with a 2nd or 3rd generation TKI. The place of alloHSCT has evolved over the last decade but nevertheless there is still a role for alloHSCT for CML patients.

Methods: The goal of frontline therapy in CML is to obtain CCyR within 12 months, then patients are monitored mainly by qPCR for BCR-ABL levels to obtain MMolR (BCR-ABL1/ABL1 < 0.1%). Patients with deep or complete molecular response that stays for years may have a try to discontinue TKI treatment as about 40% will be off

therapy without relapse thereafter. Imatinib mainly but also dasatinib and nilotinib may be used first line. However a proportion of patients will need a switch of TKI for different reasons. Patients losing CCyR should receive a different TKI. Mutations analysis of BCR-ABL should be looked at to define the best 2nd or 3rd line TKI to use but also co-morbidities to take into account specific side effects of the different TKIs. For 2nd line therapy, nilotinib, bosutinib, dasatinib or ponatinib can be chosen, depending on the 1st line treatment, mutational status and co-morbidities. In the presence of T315I mutation, only ponatinib will be efficient. Patients who received more than 2 TKIs or have a T315I mutation have a worse outcome, particularly in advanced phases (AP or CP). Only a small proportion of patients in 3rd line setting achieve CCyR (between 20–60%), the highest chance being with ponatinib.

Results: The results of alloHSCT in CP has also evolved with less NRM and long term OS of 85–90% in CP1. The survival after alloHSCT is not modified if the patient has or not received imatinib prior to transplant whatever the phase of the disease, but is worse in the presence of BCR-ABL1 mutation or in more advanced phase (>CP1, AP or BC). The number of TKI prior transplant may have an impact (>2TKI worse), but the results are conflicting.

In 2018 the recommendation for alloHSCT for CML should be as follow: patients in CP in 3rd line therapy with TKI, patients with T315I mutation after debulking with ponatinib, patients in advanced phase (AP or BC) after debulking with TKI ± chemotherapy.

Conclusions: The place of alloHSCT for CML has changed over the last decades. In 2018, patients who will need such therapy are the one in CP who are in 3rd line treatment, have T315I mutation or are in advanced phase CML (AP or BC) after debulking with TKI ± chemotherapy.

Conflict of interest: Advisory board: Novartis, BMS, Pfizer, Incyte

WP003

Long-term outcomes after alloHCT taking into account population mortality

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Background: Risk of mortality following allogeneic hematopoietic stem-cell transplantation (alloHCT) is challenging to discuss with older patients who have myelodysplastic syndromes (MDS). Post-HCT mortality may be relapse-related, treatment-related, or unrelated to MDS and its treatment (population mortality). We investigated the contribution of these causes to mortality in MDS patients who received HCT, focusing on patients who survived the first two years relapse-free.

Methods: We studied a large multi-national cohort of patients who had received an allogeneic haematopoietic stem cell transplantation for MDS or secondary acute myeloid leukaemia and whose data had been collected by the European Society for Blood and Marrow Transplantation (n = 6434). Median age at alloHCT increased from 49 years in 2000 to 58 years in 2012.

Results: Allogeneic transplantation is the only curative treatment for these patients, yet it is also associated with high mortality, due to the underlying disease, previous treatment or the transplantation itself. In this interactive workshop, we will discuss how to quantify these different elements. In particular, we will discuss the relevance of population mortality with the audience. When are data sufficient to adjudicate causes of death? And how relevant are other causes of death than disease- and treatment related death for different age groups? These questions are especially relevant for the increasing group of older patients.

Conclusions: The two major causes of failure after transplantation, relapse of the disease and non-relapse mortality (NRM), were analyzed in a competing risks model. Population hazards of mortality were estimated by matching each patient to controls from the general population with the same sex, age and nationality in the year of transplantation. We integrated the population hazards into a multi-state model to separate excess and population NRM, and excess and population death after relapse.

The presentation will show how combining relative survival and multi-state models helps to understand the different components of mortality and the impact of age on them better. Our interpretation of excess NRM as a good approximation of treatment-related mortality is an improvement of the current practice to interpret total NRM as treatment-related mortality, especially in studies with older patients.

Conflict of interest: L. de Wreede: No conflicts of interest

J. Schetelig: Lecture fees or unrestricted educational Grants from Roche, Abbvie, Janssen, Gilead and Jazz Pharmaceutical; Research support from Novartis, Sanofi, and Abbvie

WP004

Intercenter differences in the clinical and morphological diagnosis of transplant-associated microangiopathy: A study on behalf of the CQLWP of the EBMT

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Background: Transplant-associated microangiopathy (TAM) is a severe and frequently life-threatening complication of allogeneic stem cell transplantation (SCT). Thus correct laboratory confirmation and differential diagnosis are important, especially in the context of emerging new therapies, like complement inhibitors. Therefore, a practice of TAM clinical and morphological diagnosis was investigated in 17 EBMT transplant centers.

Methods: The study included two questionnaires, one for transplant physician and one for morphologist, and a set of 20 blood slide photographs of 20 cases for quantification of proportion of schistocytes. 10 of these cases represented patients with TAM, with diagnosis established based on International Working Group (IWG) criteria at the Pavlov First Saint Petersburg State Medical university and Helsinki university. The remaining 10 were control cases, including blood slides from patients with other SCT complications, non-transplant patients with myelodysplastic syndrome, autoimmune hemolysis, thalassemia, myelofibrosis and poikilocytosis due to B12 deficiency. 17 EBMT centers participated in the study. The results of the blood slide evaluation were correlated with the questionnaires and evaluated by morphologist.

Results: Based on physician's questionnaires, 41% of centers use IWG criteria, 41% – "overall TAM" criteria (Cho et al. Transplantation 2010) and 18% physician's decision for the diagnosis of TAM. For 65% of physicians the percentage of schistocytes required for the diagnosis of TAM is above 4%, for 18% above 1%, for 12% above 2%, and one center considered the level of schistocytes not important for the diagnosis. Based on morphologists's form, the morphological forms of abnormal red blood cells that were counted as schistocytes were triangular cells (in 93% of centers), helmet cells (93% of centers), keratocytes (67%), microspherocytes (53%), degmacytes (47%), stomatocytes (13%), acanthocytes (7%) and codocytes (7%).

The mean number of schistocytes reported from blood slide analysis was 42 ± 13% for TAM cases (range 0–19.6%), and 0.6% for control cases (range 0–8.3%). There were repeating intercenter differences for all cases,

indicating the differences in practices of morphological evaluation. In 95% of blood slide evaluation results each center remained within the same or adjusted quartile of schistocyte number. In the lower quartile the number of schistocytes counted was below 2% in 7/10 of TAM cases and 10/10 control cases. In the 2nd quartile the number of schistocytes counted was below 2% in 5/10 of TAM cases and 10/10 control cases. In the 3d quartile the number of schistocytes counted was below 2% in 2/10 of TAM cases and 10/10 control cases. In the 4th quartile the number of schistocytes counted was below 2% in 0/10 of TAM cases and 7/10 control cases. The morphologist's conclusions regarding the reasons behind the reported results for each quartile are presented in table 1.

Conclusions: The survey identified the significant variability in the practices of TAM morphological confirmation and revealed the need of consensus regarding the morphological definitions of schistocytes and practices of their calculation.

Conflict of interest: nothing to disclose

WP005

Incidence, severity, management and outcome of SOS/VOD after allo HCT—prospective non-interventional study

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Background: The landscape of sinusoidal obstruction syndrome / veno-occlusive disease of the liver (SOS/VOD) has changed considerably during the recent years. Conditioning regimens have greatly evolved since the time when the widely used diagnostic criteria were described. The number SOS/VOD cases that develop later than the classical time frame may have increased. New risk factors have been identified, and patients with more risk factors for this complication are currently transplanted. Most patients with milder forms recover, but severe SOS/VOD is still a very serious complication with high mortality. There have not been any satisfactory means to predict in an early phase which patients will develop severe SOS/VOD. Early prediction has become particularly important as effective treatment has become available, and early treatment has been shown to result in improved outcome. Therefore the EBMT has recently published revised diagnosis and severity criteria of classical and late-onset SOS/VOD for adult patients undergoing allogeneic transplantation (Mohty et al, 2016).

Aim: The Transplant Complications Working Party is going to carry out a prospective non-interventional study with the primary objective to determine the incidence and outcome of SOS/VOD in allogeneic hematopoietic stem cell transplantation in adult patients at the present time. Secondary objectives are to evaluate the predictive impact of the severity grading according to the new EBMT criteria on the outcome of SOS/VOD, and to evaluate the effect of severity grading on treatment decisions.

Methods: Conduct of the study: Allogeneic EBMT centres treating adult patients will be invited to participate. The study period for each participating institution will be a fixed period, one year. Patients developing SOS/VOD are reported in detail. In addition to the routine EBMT reporting, the centres report on a specific MedB/C form the SOS/VOD risk factors, SOS/VOD prophylaxis, data of diagnostic procedures, treatment and outcome. For the calculation of SOS/VOD incidence, the total number of allogeneic transplantations carried out during the study period at each participating centre is reported.

Results: The reporting for this study takes place on day +100. Later follow-up will be according to the routine EBMT reporting.

Conclusions: To avoid any publication bias, the total numbers of allogeneic transplant patients and those with SOS/VOD diagnosed will be confirmed from the EBMT registry.

Conflict of interest: nothing to disclose

On behalf of the Transplant Complications Working Party of the EBMT

WP006

Investigation and management of bone mineral density following HCT: a survey of current practice by the Transplant Complications Working Party

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Background: : Reduced bone mineral density (BMD) is a well recognised complication of haemopoietic cell transplant (HCT). International guidelines recommend DXA scanning one year after transplant in all HCT patients [1] or else specific groups of high risk patients [2,3]. Transplant related risk factors are well described including underlying disease such as ALL and medication such as steroids. Age, family history (FH) and life style issues are also relevant to the transplant patient.

Methods: A questionnaire survey was sent to all 453 centres within 48 countries registered with EBMT as of November 2016.

Results: 100 centres replied; response rates for each question varied and are indicated by the denominator. 55/100 did not conduct routine DXA screens on their patients at any time point. Of 45 centres that conducted routine post HCT screening, multiple indications were given including steroid use after (n = 21) or before (n = 9) HCT, allogeneic HCT (n = 20), low vitamin D (n = 12), all transplant patients (n = 10), hypogonadism (n = 8), low BMD prior to HCT (n = 8), FH (n = 7), immobilisation post HCT (n = 7).

Routine DXA scans were most frequently (n = 47) conducted 12 months or less after HCT. 22/91 arranged regular scans in all patients post HCT but there was no consensus on the ideal time interval ranging from every 6 months to 5 years. Steroid dose/duration triggers for DXA scanning were variable with 15 different schedules quoted. The most frequent dose trigger was 1 mg/kg given for a minimum duration of 4 weeks (7/45)

51 used a national (n = 10) or international (n = 15) guideline to guide their practise or a specific publication (n = 11). 16 different sources were cited for guidance.

71/91 respondents gave patients guidance on preventative practise post HCT. In 33 this was written guidance with an additional 13 giving verbal guidance only. The most frequent lifestyle advice was dietary: increase of vitamin D (n = 26) or calcium (n = 18).

Osteopenia was managed with calcium/vit D alone in the majority of cases (n = 54). 24 also gave bisphosphonates and 3 gave bisphosphonates alone. Osteoporosis was managed with calcium and vitamin D in 43 cases of which 25/43 also included bisphosphonates. In 18 cases bisphosphonates only were given. 12 indicated that they would give bisphosphonates in the absence of osteoporosis; the most frequent reasons cited were steroids (n = 8) or myeloma (n = 3)

Conclusions: There is some variability in existing guidelines on DXA screening after HCT between scanning all 1. HCT recipients, 2. allograft recipients, 3. adult women transplant recipients, 4. taking prolonged steroids or calcineurin inhibitors and 5. all at high risk. Nonetheless our data indicates that routine DXA scanning is underused in most centres. Where performed, the timing of routine scanning was frequently in keeping with recommendations. The trigger for DXA scanning in the context of steroids was frequently inappropriately high at 1 mg/kg daily rather than 5 mg a day for 3 months. In established osteoporosis, a combined approach of bisphosphonates with calcium/vitamin D was under-utilised.

Our data suggests that dissemination and implementation of transplant-related guidance on DXA scanning is poor and further education is required.

Conflict of interest: nothing to disclose

WP007

Pathogenesis of relapse after allogeneic hematopoietic transplantation for AML

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Background: The progress in the knowledge of pathophysiology of AML underlines that it is a very heterogeneous disease. Mutational analyses using massive sequencing techniques have revealed new genetic abnormalities involved in the development of the disease and in the emergence of leukemia relapse. AML progression follows an evolutionary process with an initial genetic event followed by additional mutations that trigger the neoplastic behavior of the disease.

Methods: At diagnosis, AML is a multi-clonal disorder with a predominant cell population. Under treatment, this predominant clone and others (but not all) are frequently sensitive to chemotherapy. The disease relapses from the predominant clone at diagnosis or from others with a different mutation pattern reflecting chemo resistance. It may happen that cells with a leukemic stem cell phenotype are enriched at relapse.

Results: The genetic factors that increase the relapse incidence and decrease survival in AML have been updated in the recent guidelines of the European LeukemiaNet. This classification recognizes three categories: low risk, intermediate-risk and high risk; the latter includes AML with the following abnormalities: t(6;9), t(v;11q23.3); t (9;22), inv(3) or t(3;3)1),del(5q); abn(17p), Complex karyotype, monosomal karyotype, wild-type NPM1 and FLT3-

ITD high ratio, mutated RUNX1, mutated ASXL1, and mutated TP53. Up to now, all of these adverse AML cases have an indication of allogeneic transplantation, although relapse incidence after conventional transplant approaches is very high, frequently above 70–80%. Despite the negative impact of the mentioned genetic alterations also on transplantation outcome, in many cases patients still have some benefit from receiving this procedure. Another important factor that increases post-ransplant relapses is the persistence of measurable residual disease before the procedure by flow-cytometry or molecular methods. This seems to be the case in patients receiving myeloblative and reduced intensity conditioning, although not all authors agree on this aspect. It has been reported that cord-blood could be the best source in case of MRD positivity, although the results need confirmation.

Conclusions: Leukemia recurrence is a major problem in patients transplanted for AML in complete remission with adverse genetic features and/or MRD persistence. Relapses are usually from recipient cells and occasionally from donor cells: in this last circumstance marrow microenvironment may have a role in predisposing the leukemia growth. Recent reports reveal that the mutation pattern after a postransplant relapse may be different to the one at diagnosis. Relapses may be favored by incomplete donor chimersim, *in vivo* or *ex vivo* T-cell depletion, mild or absent graft versus host disease, heavy immunosuppression and mainly in the haplo-transplant setting, the lack of the HLA mismatch, in the cells causing relapse, that triggered graft versus leukemia reaction.

Approaches to overcome this problem are under investigation, such as molecularly targeted therapy and hypomethylating agents, among others. Immune interventions such as early discontinuation of immunosuppressive agents plus donor lymphocyte infusions may also be helpful. Additionally new forms of more specific anti-tumor cell therapies such as the promising CAR-T cells deserve investigation; although so far have limitations in AML.

Conflict of interest: Nothing to disclose.

WP008

Novel strategies to activate NK cells and make them antigen-specific

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Background: Natural killer (NK) cells are capable of immune surveillance mediated by a balance of activating and inhibitory receptors.

Methods: We have shown that adoptive transfer of NK cells can induce complete remissions in patients with refractory acute myelogenous leukemia (AML) when combined with lymphodepleting chemotherapy and IL-2, however; one of the limitations is that IL-2 can stimulate regulatory T cells (Treg) resulting in immune suppression. We have studied the ability of IL-2/DT to eliminate Treg and more recently, IL-15, because it does not bind Treg.

Results: Using these approaches, 30–50% of patients with refractory AML attain clinical remissions as a bridge to transplant. Yet, NK cells are limited by longevity after adoptive transfer and the lack of antigen specificity. To address longevity, we have discovered that "adaptive" NK cells induced by CMV are long-lived, highly functional and exhibit properties of immune memory. In addition, we have explored IL-15/IL-15Ra-Fc (ALT-803), an IL-15 super-agonist complex, which may be more optimal to present IL-15 to the immune system. Clinically, ALT-803 induces potent stimulation of NK and CD8+ T cells in vivo and clinical responses including a complete remission lasting 7 months. This has led to a relapse prophylaxis study with ALT-803 to promote immune reconstitution after reduced intensity conditioning transplantation. To make NK cells antigen specific, we have developed trispecific killer engagers (TriKEs). We have previously shown that bispecific killer engagers (BiKEs) are capable of creating immunologic synapses between NK cells and CD33 antigens on AML and MDS targets leading to NK cell signaling through the highly potent CD16 (FcγRIII) receptor. We observed that although CD16 engagement leads to enhanced killing and cytokine production by NK cells, there is no effect on proliferation. Because IL-15 is the homeostatic factor for NK cells, we developed a TriKE that includes a modified human IL-15 crosslinker sandwiched between single chain Fv against CD16 and CD33. The 161533 TriKE was highly specific to $CD33^{+}$ targets and induced NK cell specific proliferation in vitro and in mice in vivo. This has been the motivation to brings these TriKEs to the clinic upon FDA approval, expected this summer. For those settings where endogenous NK cells are absent or suppressed, use of TriKEs will require adoptive transfer of healthy NK cells.

Conclusions: Our data suggests that adaptive NK cells can be enriched from CMV+ donors after culture with IL-15 and a GSK3b inhibitor, a novel NK cell product in phase I clinical trials. Lastly, new strategies using off-the-shelf NK cells from induced pluripotent stem cells (iPSC) are being developed and will be in the clinic by the end of the year.

This will allow multiple dosing of cryopreserved "living drugs" to treat patients with cancer. Adaptive NK cells and genetically modified iPSC NK cells expressing a high affinity ADAM17 cleavage resistance CD16 should be optimal for targeting with TriKEs or other already approved anti-cancer antibodies. In summary, NK cell based immune therapies offer great potential for off-the-shelf cell therapy strategies alone and in combination against hematologic malignancies and solid tumor cancers.

Conflict of interest: Nothing to disclose.

WP009

Unmanipulated donor T-cells—clinical outcome

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Background: Infusion of unstimulated donor-T cells (DLI) represents the oldest form of cellular immunotherapy in acute leukemia. In contrast to less aggressive malignancies, DLI given for post-transplant relapse was only successful after induction of disease control by prior chemotherapy. However, in that situation, DLI achieved similar results than a second transplant. Further, long-term remission was only achieved when chemotherapy-based remission was consolidated with DLI.

Methods: More recently, DLI was applied for relapse prevention after SCT, either as pure prophylaxis in high-risk disease, or pre-emptively to treat decreasing chimerism or minimal residual disease/molecular relapse. Both approaches have been frequently used, including multiple variations with respect do type of cells infused (pure DLI vs. stimulated PBSC+T-cells), timing, prior T-cell depletion and concomitant immunosuppression.

Results: Growing evidence is available for the efficacy of these approaches, as well as the possibility to combine DLI with innovative drugs to reduce the risk of post- transplant relapse.

Conclusions: In this talk, we will briefly review all aspects of unstimulated DLI to set a stage for more specific immune-approaches and the introduction of checkpoint inhibitors into the field.

Conflict of interest: Nothing to disclose.

WP010

Immunotherapy for prevention and treatment of relapse after SCT in AML: Immune checkpoint inhibitors

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Background: Allogeneic stem cell transplantation (allo-SCT) is the most effective curative option in adult patients (pts) with high risk acute myeloid leukemia (AML). However, disease relapse remains the major cause of treatment failure with up to 70% of the high risk AML pts still relapse. Strategies to reduce the risk of relapse post allo-SCT are consequently urgently required.

Methods: Targeting of the PD-1/PD-L1 axis may serve as one of the possible strategies. Both solid tumors and hematological malignancies develop mechanisms that enable them to evade the host immune system by usurping immune checkpoint pathways such as PD-1, PD-2, PDL-1, or PDL-2, which are expressed on activated T cells and on T-regulatory, B cells, natural killers, monocytes, and dendritic cells. One of the most exciting anticancer development in recent years has been the immune checkpoint blockade therapy by using monoclonal antibodies (MAbs) against immune checkpoint receptor and/or ligands. Anti-PD1 MAbs have been tested in clinical studies that included pts with hematological malignancies showing a remarkable efficacy mainly in Hodgkin lymphoma (HL) with emerging data in myeloma and possibly in leukemia. PD-1 blockade synergizes with autologous SCT as demonstrated in a murine model of AML where the graft versus leukemia effect (GVL), mediated via introduction of tumor-reactive T-cell receptor genes, was enhanced by combination therapy with concurrent PD-1 blockade.

Results: In the clinic, one of the first attempts in this regard was by using ipilimumab, a human anti-CTLA4 ipilimumab Mab in 29 pts relapsing after allo-SCT, initially at relatively low doses, with only 3 pts responding. Subsequently with higher doses of the MAb (10 mg per kg) out of 22 pts 5 (23%) achieved a CR, 2 (9%) a PR, and 6 (27%) decreased their tumor burden. Notably, CR occurred in 5 pts with AML (extramedullary -4, transformed—1). Four pts had a durable response for more than 1 year. Responses were associated with in situ infiltration of cytotoxic CD8+ T cells, decreased activation of regulatory T cells, and expansion of subpopulations of effector T cells in the blood. It was subsequently shown that in vitro PD-1 inhibition, increased the proliferation and cytokine secretion activity of $CD8^+$ T cells, thus substantiating a case for early

introduction of PD-1 inhibition post-transplant to reverse and enhance antitumor immunity. In a different cohort of Lymphoma pts it was demonstrated that immune reconstitution after PD-1 exposure was characterized by decreased Treg:CD4 and Treg:CD8 ratios in addition to severe and persistent depletion of PD1+ T-cells which may contribute to increased graft versus tumor response. Obviously one of the risk of this approach is an increased risk of graft-versus-host disease (GVHD) as was previously demonstrated in a murine model of GVHD in which PD-1 blockade resulted in increased mortality. A recent retrospective analysis of 39 pts with lymphoma who received prior to allo-SCT treatment with a PD-1 inhibitor conclude that there may be an increased risk of early immune toxicity, which could reflect long-lasting immune alterations triggered by prior PD-1 blockade, as the authors observed a 1-year cumulative incidences of grade 2–4 and grade 3–4 acute GVHD and chronic GVHD of 44%, 23% and 41%, respectively.

Conclusions: These data suggest that, immune checkpoint blockade holds the potential to enhance the efficacy of the GVL effect reducing relapse rate post allo-SCT however, there may be an increased risk of early immune toxicity including GVHD. The results of ongoing and future clinical trials will help in establishing the exact role PD-1 blockade post allo-SCT.

Conflict of interest: Nothing to disclose.

WP011

Treating Acute Leukemia with CAR-T cell and antibodies

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Background: The bispecific antibody blinatumumab and the adoptive transfer of CD19-specific chimeric antigen receptor engineered T cells (CAR T cells) resulted in encouraging clinical trials in ALL. Several new constructs are on the way targeting epitopes of AML (CD33, CD123). However, there are certain limitations of the fascinating CAR T cell technology. CAR T cells can lead to even life-threatening off-tumor, on-target side effects if CAR T cells crossreact with healthy tissues. Several concepts are developed to overcome these problems.

Methods: We designed a modular universal CAR platform technology termed UniCAR that reduces the risk of on-target side effects by a rapid and reversible control of CAR T-cell reactivity.

Results: The UniCAR system consists of two components: (1) a CAR for an inert manipulation of T cells and (2) specific targeting modules (TMs) for redirecting UniCAR T cells in an individualized time- and target-dependent manner. UniCAR T cells can be armed against different tumor targets simply by replacement of the respective TM for (1) targeting more than one antigen simultaneously or subsequently to enhance efficacy and (2) reducing the risk for development of antigen-loss tumor variants under treatment.

Conclusions: Current available in vitro and in vivo data will be presented.

Conflict of interest: Nothing to disclose

WP012

Europe-wide survey on the use of thrombopoietin agonists for the treatment of aplastic anemia

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Background: Thrombopoietin (TPO) agonists such as eltrombopag (ELT) emerged recently as a novel therapeutic option to complement standard aplastic anemia (AA) treatment consisting of immunosuppression (IS) with anti-thymocyte globulin (ATG) and cyclosporine A (CyA), as well as allo-HSCT in eligible patients. How TPO agonists are used outside of clinical trials in the real-world setting and results of this treatment are not known.

Methods: We conducted a retrospective survey on the use of TPO agonists for AA among EBMT member centers. We included the dataset on ELT-treated patients from France recently published by Lengline ***et al***., Haematologica 2017. 180 patients from 45 centers were reported. We analyzed 151 patients having received at least 30 days ELT and having a follow up of at least 2 months. Patients with a shorter duration of treatment or follow up, as well as three patients receiving romiplostim were excluded.

Results: The reported ELT treatment episodes were 2012 to mid 2017, 89% of patients are alive at a median follow up of 12 months. ELT was applied both as part of the first-line treatment and in relapsed or refractory patients, either as a monotherapy or in combination with CyA +/-ATG. The reasons for ELT use and for the choice of particular combination regimens is not known, given the retrospective nature of the survey. Compared to lower intensity treatment (ELT alone or in combination with CyA), patients treated with ELT/CyA/ATG in the first line setting were younger and had more severe AA (Table 1). Overall, most ELT treated patients (89%) were platelet transfusion dependent, suggesting platelet recovery as an important goal of ELT treatment.

The overall response rate (ORR) varied between 42% and 86% across treatment groups (Table 1), likely reflecting differences in patient selection. Interestingly, the ORR to ELT was similar in relapsed or refractory patients if used alone or in combination with CyA ($p = n.s.$). Although 53% of the patients stopped ELT, only 16% patients received further non-transplant treatment, showing the lack of meaningful treatment options in patients not responding to IS and ELT. 25 patients (17%) underwent allo-HSCT at a median of 202 days following start of ELT. Whether ELT was useful as a bridge to transplant or was simply applied to relapsed/refractory patients with an indication for allo-HSCT is not known.

At the median ELT dose of 150mg/day, adverse events were infrequent and consistent with the known safety profile of ELT. No new adverse effects were reported

Conclusions: ELT, is used widely in Europe to treat AA patients. Although early adoption of this novel therapy led most likely to negative selection of AA patients, the results of ELT treatment in the real world setting are consistent with the reported clinical trial data.

Conflict of interest: nothing to disclose

	1st line		Failure/PR after 1st line			Relapse		
	ELT or ELT/CyA	ELT/CyA/ATG	ELT	ELT/CyA	ELT/CyA/ATG	ELT	ELT/CyA	ELT/CyA/ATG
n=	14	17	24	48	5	16	10	7
Age at ELT start (median in years)	62.7	32.3	66.8	38.6	7.7	43.9	40.7	48.0
AA severity before ELT treatment (SAA/vSAA)	38%/31%	65%/24%	57%/13%	70%/11%	80%/20%	80%/13%	100%/0%	100/0%
Interval diagnosis to ELT treatment (median in months)	2.8	2.9	20.6	8.9	4.4	50.4	56.6	10.0
ORR (CR/PR)	43% (21%/21%)	59% (29%/29%)	43% (17%/26%)	42% (19%/23%)	60% (20%/40%)	53% (0%/53%)	50% (20%/30%)	86% (14%/71%)
ELT treatment ongoing	71%	41%	58%	29%	20%	50%	50%	71%
Any further non-HSCT therapy	29%	12%	8%	17%	40%	13%	10%	

[[WP012 Table] Table 1]

WP013

Russian experience in HSCT for autoimmune diseases

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Background: Russian Federation is country with total population of 150 mill ion. Most common autoimmune disorder (AD) in Russia is multiple sclerosis (MS) with more than

150 000 of patients registered. Some of adults and children with AD require hematopoietic stem cell transplantation (HSCT).

Thus, objective was to estimate long-term outcomes and late effects in adults and children with MS and neuromyelitis optica (NMO) after HSCT

Methods: It were 16 children included (MS—13, NMO—3). MS: female—9, male—4; NMO: all females. MS median age—16,8 ± 1,6 y.o., median EDSS 6,16 ± 0,2. NMO pts. median age—12,7 ± 1,4 y.o. All patients had severe refractory disease. MS children received Cyclophosphomide and ATGAM, NMO—Treosulfan, Fludarabine, Rituximab and ATGAM. All children treated in the Russian Children's Research Hospital in collaboration with Dmitry Rogachev Center. Nighty nine MS adults received HSCT in National Pirogov Medical Surgical Center with the help of reduced-intensity BEAM-like conditioning regimen in mean age—35 years old; male/female—39/60; median Expanded Disability Status Scale (EDSS) = 3.5; 43 relapsing/remitting MS, 56 progressive MS. Twenty five MS adult patients were transplanted in Raisa Gorbacheva Institute in 2000–2010 in mean age of 36 years old with the help of BEAM+ATG regimen.

Results: In children EDSS improved at MS patients fast—on 3,1 ± 0,3 during first 60 days. Median follow-up 48,7 ± 2,4 months (10–84 months). Two MS patients relapsed (clinical and MRI). NMO patients stopped the progression and improved neurologically (clinical and MRI). One pt. with NMO died due to refractory ADV-infection, two patients did not have any severe toxic episodes. Median follow-up 23 ± 4,7 months (1- 60 months). MS patients late effects: cardio-vascular—5 pts., endocrine—3 pts (all females). NMO patients late effects: cardio-vascular—2 pts., late immune reconstitution—1 pt. In Pirogov Medical Surgical Center group at 6 months post-transplant, neurological improvement or stabilization was observed in all the patients except one. Cumulative incidence of disease progression was 16.7% at 8 years after HSCT. Sixty-four patients who did not progress during the first 3 years post-transplant and were monitored for more than 3 years were included in long-term outcome analysis. At the median long-term follow-up of 62 months, 47% of patients improved by at least 0.5 points on the EDSS scale as compared to baseline and exhibited improvement during the entire period of follow-up; 45% of patients were stable. In Raisa Gorbacheva Institute group 50% of patients relapsed. No transplantrelated deaths and severe complications were observed both in children and adults.

Conclusions: HSCT in Russia used both for children and adults. It is successful approach for refractory MS and pediatric NMO treatment. In-time HSCT can significantly improve the outcome. Late effects can be found in these patients, so it's important to find it and give adequate rehabilitation. Thus, the risk/benefit ratio of HSCT with in our population of patients is very favorable. Registration in EBMT database should be optimized.

Conflict of interest: No conflicts of interest to declare.

WP014

Infectious Diseases Working Party EBMT activity 2017–2018: analysis of abstracts submitted for Annual Meeting

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Background: Infectious Diseases Working Party (IDWP) EBMT is a transversal Working Party, with scientific interests involving infectious complications in patients undergoing hematopoietic stem cell transplantation, regardless on primary diagnosis. The mission of IDWP is: (1) to organize high level accredited educational activities related to infectious diseases of HSCT; (2) to design and support prospective studies in the field of infectious diseases; (3) to generate high quality retrospective studies and surveys addressing different issues related to infectious diseases management and therapy; (4) to generate guidelines related to the management of infectious diseases.

Methods: Currently ongoing prospective non-interventional studies run by IDWP: (1) Current treatment of HCV infection after HSCT, (2) Impact of pre-existing invasive aspergillosis on allogeneic stem cell transplantation (IPAT), (3) Pneumocystis jirovecii pneumonia (PcP) after allogeneic HSCT, (4) infections related to CVC placement.

Results: This report summarizes also general data of abstracts submitted to EBMT-2018 Annual Meeting: infectious diseases every year belongs to the Top-3 areas of interest. A total number of 96 abstracts were submitted for infectious complications for EBMT-2018. Their characteristics: 55 (62%) retrospective studies, 31 (35%) prospective studies: 24 (25%) abstracts reported the results of multicenter studies (including 4 RTC Phase II and Phase III studies; 6 studies from EBMT-IDWP: and a total of 10 international studies), 6 (6.3%) were case reports, 2 in-vitro study and 1 meta-analysis. 69 (75%) abstracts concerned

adults, 15 (16%) children, and 8 (9%) mixed populations. 60 abstracts (64%) focused on allogeneic transplant, 10 (10.6%) on autologous transplant, 24 (25.4%) on auto- and allo-transplants. Viral infections were studied in 51 (53%) abstracts (including 4 abstracts related to: letermovir, brincidofovir or presatovir), fungal infections in 14 (14.6%), bacterial infections in 20 (28%) (including fecal microbiota transplantation in 1 abstract), parasite 3, and various infections in 8 (8.3%); with vaccination being the focus in 2 abstracts. The objective of 47 (49%) abstracts was epidemiology/risk factors/outcome, diagnosis in 9 (9.3%), prophylaxis in 11 (11.5%), immunity in 6 (6.3%) including CAR-T cells against CMV, therapy in 17 (17.7%), and economy in 1 (1%) abstract.

Conclusions: In comparison to EBMT-2017, more abstracts were based on multicenter, nationwide (Poland, Spain, Italy, France, Japan) or international studies, and there was an increase in number of studies focused on viral or multiple infections. Significant decrease in number on fungal topics was noted, however a new drug rezafungin was reported in two *in vitro* studies.

Conflict of interest: All authors declare no conflict of interest

WP015

Ongoing studies within Infectious Diseases Working Party (IDWP) of EBMT

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Background: Scientific activity is the fundamental part of IDWP and IDWP studies address both frequent and rare post-transplant infectious complications. Additionally, surveys on the management of selected infections, prevention measures and treatment strategies help us in gaining insight into these important issues.

Methods: The following prospective non-interventional studies are currently run by IDWP: (1) Current treatment of HCV infection after HSCT, (2) Impact of pre-existing invasive aspergillosis on allogeneic stem cell transplantation (IPAT), (3) *Pneumocystis jirovecii* pneumonia (PjP) after allogeneic HSCT, (4) CVC-associated infections depending on the site of insertion (IDWP and NG study).

Results: The study on HCV is focused on patients who are HCV-RNA positive at post-transplant visit occurring between December 2015 and December 2017 with particular attention on the use of recently introduced directly acting antivirals (DAAs). Data from 48 patients from 15 centres have been reported so far.

The IPAT study explores the impact of pre-HSCT aspergillosis in patients with acute leukaemia and MDS. As of January 2018, 850 patients, including 58 IA cases (incidence 6.8%), have been reported and the study period has been extended until May 2018.

The study on pneumocystosis started in March 2016. Although 109 centres showed their interest, 23 cases have been enrolled so far. In order in increase the number of patients, a retrospective collection of cases occurring after March 1st 2016 has been allowed. The main inclusion criteria are the first diagnosis of pneumocystosis documented in a BAL fluid, whatever the positive diagnostic test (cytology, IF or PCR) and whatever the presentation and treatment, in a patient who received allogeneic HSCT within the previous 24 months.

The study on the risk of infectious complications in adult patients after HSCT depending on the site of central line insertion (jugular vs. subclavian) has been launched in October 2017 and enrolled 61 patients.

Retrospective studies run by IDWP and usually registry-based and have recently focused on the following pathogens: CMV, EBV, JCV, ADV, HHV6, HHV8, *Candida, Legionella spp., Toxoplasma gondii, Mycobacterium tuberculosis* and on the causes of deaths after HSCT. For some of these studies, centres who reported cases are contacted by IDPW office in order to provide additional information and improve the scientific quality of the study.

Conclusions: Ongoing or recently completed surveys address prevention practices, the use of antibiotics, the management of adenovirus infections, and, in collaboration with the Nurses Group, the protective environment issues. When developing a survey, we focus on gaining maximum information with the least possible time needed to complete the survey. Wide participation and identifying a dedicated team member in every centre are fundamental for a successful result.

Specific forms for proposing a new prospective or retrospective study to IDWP are available from the IDWP office at *idwp.ebmt@lumc.nl*.

Conflict of interest: All authors declare no conflict of interest

WP016

ECIL 7 vaccination guidelines for HSCT recipients

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Background: Autologous and allogeneic HSCT recipients are at high risk of infection, and some of these infections are vaccine-preventable. Many transplant patients are able to respond to vaccine, even early after transplant for the more immunogenic vaccines such as pneumococcal conjugate vaccine (PCV). Although the clinical efficacy of vaccines has been rarely shown except for influenza inactivated vaccine (IIV), it is of paramount importance to have systematic programs of vaccination as it may avoid infections, or at least decrease their severity. Additionally to the individual benefit, this should contribute to herd immunity which is actually compromised for some diseases, due to reluctance to vaccination in some countries.

Methods: The ECIL 7 meeting addressed the issue of vaccination in hematology patients, including HSCT recipients and graded its recommendations according to ESC-MID. The slide sets are available at www.ecil-leukaemia.com/ since October 2017.

Results: When compared to the more recent guidelines (Ljungman et al. 2009; Rubin et al, 2013), the main changes are the following: (1) For PCV: we still recommend 3 doses, one month apart, from 3 months after transplant (AIr), but now either a 4th PCV dose in case of GvHD, around 6 months after the last PCV dose (BIIu), or one dose of pneumococcal polysaccharide 23-valent vaccine at 12 months if no GvHD (BIu). (2) For *N. meningitis*: despite few data, we recommend a C (BIIu) and B (BIIIu) vaccination from 6 months after transplant. (3) For Flu: IIV remains recommended from 6 months after allogeneic HSCT, yearly, and as long as the patient is considered immunosuppressed (AIIr) or life-long (BIIr), and from 6 months after autologous HSCT, as long as the patient is considered immunosuppressed (BIIr). (3) HBV vaccine is recommended from 6 months after transplant according to country recommendation and age, or on the basis of antiBHs titers to prevent reverse seroconversion. (4) For Human papilloma virus (HPV) vaccine, young HSCT recipients should benefit of this vaccination according to country recommendation (BIIu). No change was proposed for *H. influenzae*, tetanus, diphtheria, poliomyelitis vaccine except for adding pertussis toxoid to DT vaccination, 3 doses at 1 month interval (CIIIu). When rituximab has been administered, vaccination should be postponed at least 6 months after the last dose. We do not recommend to postpone vaccination in case of GvHD or until recovery of biological parameters such as lymphocyte or CD4 counts, except in case of severe hypogammaglobulinemia (< 3g/L), leukemia relapse, or uncontrolled grade 3–4 GvHD. These patients should benefit of additional measures such as antibacterial prophylaxis, until improvement. There is no evidence of more safety issue after HSCT than in the healthy individuals, and especially no evidence that vaccine may trigger or increase GvHD in prospective trials. Data are limited to recommend specific long-term programs. Assessing the specific antibody titers after the initial program should help in deciding for boost on an individual basis.

Conclusions: The donor vaccination seems to be of marginal benefit and anyway difficult to apply in most cases.

Conflict of interest: nothing to disclose

WP017

Pulmonary complications in Hematopoietic Stem Cell Transplantation

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Background: Pulmonary complications (PC) occur in over one-third of patients post-HSCT and are responsible for 50% mortality not associated to infections. PC include several entities and the most relevant are described.

There is a timeline of PC following HSCT, divided in three phases, each of which has it main host immune system defect. Also in each phase there is a distinction between infectious and non-infectious complications.

Bacterial pneumonia is the most frequent infectious complication, but viral infections, with its own cronological appearance, have important morbidity and mortality. The most frequent virus is respiratory syncitial virus, followed by parainfluenza, influenza and adenovirus. In 30–50% these virus are co-pathogens with CMV and/or Aspergillus.

Methods: Non-infectious complications have a broad clinical spectrum after HSCT. We can distinguish between acute lung injury and late onset non-infectious pulmonary complications (LONIPC).

Among acute lung injury, congestive heart failure, idiopathic pneumonia syndrome (IPS)—that includes different entities and has a distinctive definition and diagnostic criteria- and diffuse alveolar hemorrhage are the more relevant conditions. Its pathogenesis is poor understood.

Results: Due to better supportive care measures, there are less infectious complications with better survival and an increased incidence of LONIPC. *Bronchiolitis obliterans* syndrome (BOS) is the most common late complication. This entity will be extensively discussed, emphasizing therapeutic approaches. Cryptogenic-organizing pneumonia (COP) is the other relevant LONIPC. COP is a distinctive entity and differential diagnosis is very important between COP and BOS.

Conclusions: Finally, the diagnosis work up of PC is discussed and the author presents a prospective study of PC in HSCT. A multidisciplinary approach of Pneumologist, Hematologist, Radiologist, Pathologist and Microbiologist would improve the care of the patients with PC.

Conflict of interest: Nothing to disclose.

WP018

Abstract previously published