Recent developments and future directions in hematopoietic stem cell transplantation and cellular therapy.

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Recent developments and future directions in hematopoietic stem cell transplantation and cellular therapy.

A personal digest of the Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT) 2019 in Frankfurt, Germany.

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Abstract

From March 23 to 27 2019 the 45th Annual Meeting of the European Society for Blood and Marrow Transplantation 2019 was held in Frankfurt, Germany. Along with the common topics of allogeneic hematopoietic stem cell transplantation (alloHSCT) such as improvements in conditioning regimens, treatment of graft-versus-host disease (GvHD) and reducing the risk of malignant relapse, a particular emphasis of the meeting was put on the rapidly expanding field of chimeric antigen receptor T cells (CAR T cells). The following article poses a personal selection of recent developments covered at the meeting.

Conditioning regimens and eligibility for alloHSCT

On behalf of the International MC-FludT.14/L study group Dietrich Beelen presented the results of a prospective randomized phase-III-trial to compare Treosulfan/Fludarabine and reduced-intensity Busulfan/Fludarabine as conditioning regimen for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [1]. 476 patients in total with a median age of 60 years with AML or MDS in complete remission were enrolled and 1:1 randomly assigned either to the treosulfan (10g/m^2, day -4 to day -2) or busulfan (4 x 0,8mg/kg/day, day -4 to day -3) arm.
Event-free survival at two years after HSCT as the primary endpoint of the study was significantly improved with the treosulfan based conditioning regimen as compared to busulfan with 65.7% versus 51.2%, respectively (HR 0.69 95% CI).

The VidazaAllo study, a prospective multicenter phase III study comparing 5-azacytidine (5-Aza) induction followed by alloHSCT compared to continuous 5-Aza according to donor availability in elderly MDS patients (age: 55-70 years) was presented by Uwe Platzbecker on behalf of the German MDS Study Group and the German Cooperative Transplant Study Group and received the Van Bekkum Award 2019 [2]. The study recruited 170 patients all of whom received four cycles of 5-Aza. If a matched donor was available, patients underwent alloHSCT, otherwise 5-Aza treatment was continued. Patients in the alloHSCT showed significantly improved 3-year overall survival of 49% compared to 22% in the 5-Aza group (P-value 0.027). This survival benefit demonstrated by the study may have a major impact on treatment of MDS in the elderly.

Prevention and management of acute graft-versus-host disease (GvHD)

Acute GvHD still poses a major cause of transplant related morbidity and mortality, thus strategies to prevent and treat acute GvHD are urgently needed.

An innovative and promising new strategy that was presented by Muna Qayed was a phase II clinical trial with the extracellular cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) domain fusion protein abatacept for acute GvHD prevention in HLA matched (8/8 HLA match) and mismatched (7/8 HLA match) unrelated donor transplantation [3]. Abatacept (10mg/kg day -1, +5, +14, +28) or placebo was given in addition to standard GvHD prophylaxis with methotrexate and a calcineurin inhibitor. Interestingly, both the 8/8 and the 7/8 abatacept groups showed significantly reduced acute GvHD rates and disease-free survival when compared to matched donor transplant not only demonstrating efficacy of abatacept in the prevention of acute GvHD but also suggesting to change the risk of mismatched transplant to that of matched transplant by adding abatacept.

Another highly discussed avenue to treat acute GvHD was the inhibition of tyrosine kinases in particular JAK/STAT, MEK/ERK and Aurora Kinase A [4]. While it has been previously reported that JAK2 inhibitors like ruxolitinib show efficacy in the treatment of steroid refractory aGvHD (SR aGvHD) [5], the REACH1 trial is the first prospective phase II clinical trial investigating the use of ruxolitinib in SR aGVDH. The primary outcome of this ongoing single-arm study is the overall response rate at day 28 with multiple secondary endpoints such as 6-month duration of response, relapse of the underlying malignancy, non-relapse mortality, overall survial and safety [6]. The 6-month follow up data presented by Madan Jagasia demonstrated an overall response rate of 54.9% by day 28 with 68% of the patients exhibiting grade III/IV aGvHD at enrollment. The best response at any time point during treatment was 73.2%, thereby confirming ruxolitinib as a promising treatment strategy for SR aGvHD.

In addition, the selective JAK1 inhibitor itacitinib has been recently investigated in a phase I study for the treatment of steroid naïve aGvHD and has shown encouraging results and is now further tested in phase II and III studies [7]. The selective JAK1 inhibition might allow for less off-target toxicity including myelosuppression, since JAK2 signaling is crucial for hematopoiesis, whereas recent preclinical studies suggest JAK1 inhibition as the main mediator of response in aGvHD [8].

Recent preclinical studies that were also presented at the conference by John di Persio point out that the balance between JAK1 and JAK2 inhibition may be key for the control

of aGvHD and therefore found that the next generation JAK inhibitor baricitinib that exhibits a balanced IC50 JAK1/JAK2 ratio was superior at preventing aGvHD compared to ruxolitinib in mouse models. Intriguingly, mice treated with baricitinib were even able to mount significantly improved GvL responses, which might mechanistically be linked to reduced programmed cell death 1 ligand 1 (PD-L1) expression on antigen presenting cells and malignant cells mediated by baricitinib [9].

Improvement of immune reconstitution

Although alloHSCT is a potentially curative treatment option for various malignant and non-malignant hematologic diseases it often involves prolonged functional T cell deficiency putting the patients at risk for opportunistic infections, malignant relapse and overall increased mortality [10-12]. It has been previously demonstrated that patients with superior thymic function measured by T cell receptor excision circles (TRECs) show better overall survival, less bacterial and viral infections and less acute and chronic GvHD [13]. For these reasons strategies to boost thymic function after alloHSCT are of high clinical significance to improve the outcome of transplant patients.

Recently discovered pathways involved in thymic regeneration that can potentially be utilized to further enhance immune reconstitution include sex steroid ablation via induction of the Notch ligand Dll4, interleukin-22 produced by innate lymphoid cells and BMP4 produced by thymic endothelial cells as highlighted by Enrico Velardi and Ronjon Chakraverty [14-18]. Another strategy to improve post-transplant immunity involves adoptive transfer of immune cells such as T cells or NK cells. To this end, Wolfgang Herr outlined the concept of TCR transgenic CD8 and CD4 T cells to confer a more selective GvL effect by targeting antigens such as HLA-DP or the cancer testis antigene PRAME [19]. This could further be complemented by the prophylactic infusion of multi-antigen specific T cells for the prevention of viral infections early after alloHSCT, which was presented by Marthe Roex [20].

In addition, the adoptive transfer of IL-15/IL-21 activated NK cells provides a therapeutic option to boost antitumoral immunity following alloHSCT as highlighted by Evelyn Ullrich [21].

Malignant relapse

While alloHSCT poses a potentially curative treatment option, the leading cause of treatment failure remains relapse of the underlying hematologic malignancy [22].
Thus, strategies to prevent relapse and further enhance the graft-versus-leukemia (GvL) effect are critically relevant in an alloHSCT setting.
To tackle this challenge of dynamic competition between GvL response and malignant relapse several fundamental strategies have to be considered including optimization of the cytoreductive conditioning, selection of the stem cell source, reducing immune evasion and control of remaining malignant cells by customized maintenance therapy and eventually implementing novel and more effective salvage therapies, as highlighted by Charles Craddock [23].
The fundamental principle of alloHSCT exerting an antileukemic effect is the GvL response mainly mediated by donor derived T cells [24]. The concentration of this "drug" however is still more or less ignored with variations of 50-1000 cells/ kg x 10^6. Hence, clinical guidelines implementing more standardized T cell counts in combination with more precise antithymocyte globuline (ATG) changing from dosing on lymphocyte counts rather than body weight might lead to a more favorable balance between GvHD and relapse rate as emphasized in a presentation by Jürgen Kuball [25].
A novel salvage therapy that was shown at the meeting by John Craddock was the combination of 5-Azacytidine and Lenalidomide [23]. While Lenalidomide alone has been shown to worsen aGvHD, 5-Azacytidine has been proposed to mitigate aGvHD in preclinical alloHSCT models. In this phase-I trial the combination therapy of 5-Aza and lenalidomide was well tolerated and safe and 7/15 patients achieved a major clinical response to treatment. However, further evaluation in prospective trials will be needed.

To apply individualized therapies a better understanding of the underlying pathophysiological mechanisms of relapse after alloHSCT is urgently needed. To this end, Luca Vago presented recently published data on immune signatures driving leukemic immune escape and relapse [26-27].

As part of continued clonal evoluation of leukemic blasts in AML after alloHSCT not only downregulation of class II HLA-molecules such as HLA-DR, -DP and -DQ on leukemic blasts due to downregulation of the class II regulator CIITA was observed, but also drastic deregulation of T cell costimulation with concomitant T cell exhaustion in effector and early differentiated T memory stem cells (T_{scm}) and central memory T cells (T_{cm}).

Importantly, the deregulation of HLA-II molecules and of coinhibitory ligands was largely non-overlapping in the relapsing patients leading to direct therapeutic implications.

While relapse with non-genomic loss of HLA-II molecules could be approached by the induction of interferon-gamma release such as in mild GvHD or administration of interferon-gamma itself, patients with upregulation of costimulatory molecules would be more prone to immune checkpoint blockade on the other hand.

Patients with genomic HLA haplotype loss would not benefit from either of these strategies nor from donor lymphocyte infusions (DLI). Thus, such patients might be evaluated for novel therapies including bispecific antibodies (BiTes) or CAR T cell therapy.

Cellular therapy: CAR-T cells and beyond

The field of CAR T cell therapy has been moving forward to an unprecedented extent, which was also mirrored by the high degree of attention devoted to the recent developments in this field at the Annual meeting of EBMT 2019.

An evolving strategy of expanding the armamentarium in the field of CAR therapy, that has been recently translated into a first in human trial is the use of CAR NK cells which was presented by Katy Rezvani [28]. An obvious advantage of this approach compared to CAR T cells is that they can be engineered as an off-the-shelf product, since they

lack GvHD causing potential. Of note, as opposed to CAR T cells they still retain intrinsic signaling capacity through their native receptors potentially allowing them to recognize cancer cells even after downregulation of the CAR target antigen [29].

For the study, cord blood derived NK cells are genetically engineered to express a CAR targeting lymphoid malignancies (CLL, NHL, ALL) and are administered after cyclophosphamide/fludarabine lymphodepletion. Interestingly, so far none of the patients experienced cytokine release syndrome or neurotoxicity and CAR NK cells are detectable for up to 6 months post infusion. 6/9 patients reached a CR and one patient a PR [28].

Given the recent clinical success of CD19 CAR T cell therapy in B cell malignancies, extensive efforts are now being made to tailor this therapy to the treatment of solid tumors. For that to happen, Hinrich Abken gave an overview of next generation CAR T cells that modulate the tumor microenvironment by their secretion of specific cytokines. These socalled TRUCKs (T cells redirected for antigen-unrestricted cytokine-initiated killing) might be utilized to overcome e.g. TGF-β mediated repression of CAR T cells by solid tumor lesions by inducible release of IL-7 and an artificial IL7R/IL-2Rβ providing resistance to TGF-β [30].

An innovative approach for predicting response to CAR T cell therapy by analyzing the intestinal microbiome composition and thereby identifying biomarkers was presented by Melody smith and recognized with the basic science award. In particular, 25 patients with ovarian cancer, multiple myeloma (MM) or diffuse large B cell lymphoma (DLBCL) receiving MUC16, BCMA or CD19 CAR T cells respectively were included. To identify potential biomarkers, microbiome samples (fecal) were collected before CAR T cell infusion and weekly after and then underwent 16S sequencing and metagenomic shotgun sequencing. Patients who achieved a CR showed an abundance of the bacterial family lachnospiraceae, whereas patients who did not achieve CR had an enrichment in peptostreptococcaceae and increased abundance of genes associated with members of the vitamin B family [31]. Overall these findings might eventually lead to a better prognostication of CAR T cell therapy response.

Concluding remarks

The field of hematopoietic stem cell transplantation and cellular therapy has achieved seminal improvements during the last year which could only be covered to a small extent in this personal selection.

Overall, these advancements in alloHSCT together with the upcoming novel cellular immune therapies such as CAR T cell therapy outlined at the Annual Meeting of the EBMT 2019 represent a big step forward towards more efficient and less toxic therapies for patients with hematologic malignancies.

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References

1. Beelen D., Presidential Symposium, 2019 March 25, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Improved survival of AML and MDS patients after treosulfan-based compared to reduced intensity busulfan-based conditioning regimen for allogeneic haematopoietic cell transplantation: final results of a prospective randomized phase-III trial.
2. Platzbecker U., Opening Ceremony, 2019 March 24, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: 5-Azacytidine (5-Aza) induction followed by allogeneic stem cell transplantation versus continuous 5-Aza in elderly MDS patients (55-70 years). A prospective randomized study (VidazAllo study).
3. Qayed M., Oral session: GvHD clinical, 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: T cell costimulation blockade with abatacept for acute graft-versus-host disease prevention in matched and mismatched unrelated donor transplantation: results of the first phase 2 trial.
4. Blazar B., Workshop: Treatment options for patients with steroid refractory graft-versus-host disease, 2019 March 25, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Kinase inhibitors for treating patients with steroid refractory acute graft-versus-host disease.
5. Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia. 2015;29(10):2062-8.
6. Jagasia M., Oral Session: GvHD clinical, 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-versus-host disease: 6-month follow-up data from the phase 2 reach trial.
7. Sociè G., Industry Symposium: New avenues for treatment of acute GvHD and investigational therapies, 2019 March 25, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Investigational treatmens: what`s next?

8. Hill, L., Alousi, A., Kebriaei, P., Mehta, R., Rezvani, K., & Shpall, E. (2017). New and emerging therapies for acute and chronic graft *versus* host disease. *Therapeutic advances in hematology*, *9*(1), 21–46. doi:10.1177/2040620717741860
9. Di Persio J., GvHD pathophysiology and treatment, 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Inhibition of JAK pathway to treat and prevent GvHD.
10. Krenger W, Blazar BR, Holländer GA. Thymic T-cell development in allogeneic stem cell transplantation. Blood. 2011;117(25):6768-76.
11. Wils E-J, van der Holt B, Broers AEC, Posthumus-van Sluijs SJ, Gratama J-W, Braakman E, et al. Insufficient recovery of thymopoiesis predicts for opportunistic infections in allogeneic hematopoietic stem cell transplant recipients. Haematologica. 2011;96(12):1846-54.
12. Chaudhry MS, Velardi E, Malard F, van den Brink MR. Immune Reconstitution after Allogeneic Hematopoietic Stem Cell Transplantation: Time To T Up the Thymus. J Immunol. 2017;198(1):40-6.
13. Clave E, Rocha V, Talvensaari K, Busson M, Douay C, Appert ML, et al. Prognostic value of pretransplantation host thymic function in HLA-identical sibling hematopoietic stem cell transplantation. Blood. 2005;105(6):2608-13.
14. Velardi E, Tsai JJ, Holland AM, Wertheimer T, Yu VW, Zakrzewski JL, et al. Sex steroid blockade enhances thymopoiesis by modulating Notch signaling. The Journal of experimental medicine. 2014;211(12):2341-9.
15. Dudakov JA, Hanash AM, Jenq RR, Young LF, Ghosh A, Singer NV, et al. Interleukin-22 drives endogenous thymic regeneration in mice. Science. 2012;336(6077):91-5.
16. Wertheimer T, Velardi E, Tsai J, Cooper K, Xiao S, Kloss CC, et al. Production of BMP4 by endothelial cells is crucial for endogenous thymic regeneration. Science Immunology. 2018;3(19):eaal2736.
17. Velardi E., Immune reconstitution: monitoring and options for improvement, March 26 2019, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Strategies to enhance immune reconstition following SCT.
18. Chakraverty R. Acute GvHD- pathomechanism, prevention and treatment. 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Barriers to restoration of immune homeostasis following GvHD.

19. Herr W. Immune reconstitution: monitoring and options for improvement, 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Adoptive transfer of leukemia reactive T cells.
20. Roex M. Cellular therapy, 2019 March 27, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Prophylactic infusion of multi-antigen-specific T-cell products to prevent complications early after T-cell depleted allogeneic stem cell transplantation: a phase I/II study.
21. Ullrich E. Immune reconstitution: monitoring and options for improvement, 2019 March 26, 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: NK cell reconstitution after stem cell transplantation.
22. Barrett, A. J., & Battiwalla, M. (2010). Relapse after allogeneic stem cell transplantation. *Expert review of hematology*, *3*(4), 429–441. doi:10.1586/ehm.10.32
23. Craddock C. Educational Session: Strategies to optimize the GVL effect. 2019 March 25. 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany
24. Kolb H-J. Graft-versus-leukemia effects of transplantation and donor lymphocytes. Blood. 2008;112(12):4371-83.
25. Kuball J. Cell therapy day: Immune cells engineering. 2019 March 25. 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Practical considerations in DLI engineering.
26. Toffalori C, Zito L, Gambacorta V, Riba M, Oliveira G, Bucci G, et al. Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nature medicine. 2019;25(4):603-11.
27. Vago L., Relapse after transplant for acute leukema. 2019 March 27. 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: HLA loss and clonal evolution.
28. Rezvani K., New developments in the field of CAR T cell therapy. 2019 March 26. 45thAnnual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Off-the-shelf CAR NK cells for the treatment of hematologic malignancies.
29. Rezvani K, Rouce R, Liu E, Shpall E. Engineering Natural Killer Cells for Cancer Immunotherapy. Mol Ther. 2017;25(8):1769-81.

30. Abken H., New developments in the field of CAR T cell therapy. 2019 March 26. 45th Annual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: CAR T-cells against solid tumors. TRUCKs on the road.
31. Smith M. Opening Ceremony. 2019 March 24. 45th Annual Meeting of the European Society for Blood and Marrow Transplantation, Frankfurt, Germany: Intestinal microbiome analyses identify biomarkers for patient response to CAR T cell therapy.