Medicom International Conference Series in Haematology

EBMT Annual Meeting 2023

European Society for Blood and Marrow Transplantation

23-26 APRIL 2023 • PARIS • FRANCE

PEER-REVIEWED CONFERENCE REPORT

Promising novel target for AML identified

In acute myeloid leukaemia, vasoactive intestinal peptide (VIP) receptor antagonist peptides were associated with the induction of protective immunologic memory in mice with leukaemia and activated human T cells in vitro.

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Improved PFS with Ide-cel in RRMM

Idecabtagene vicleucel outperformed standard regimens in patients with triple class-exposed relapsed and refractory multiple myeloma in the phase 3 KarMMa-3 study.

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Long-term success for CAR T-cell therapy in CLL

CAR T-cell therapy may be a solution for a subset of patients with heavily pre-treated, high-risk, ibrutinib-intolerant, relapsed or refractory chronic lymphocytic leukaemia, long-term results showed.

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ISSN 2468-8762 23:09

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Letter from the Editor

Dear Reader,

It is my great pleasure to introduce this peer-reviewed EBMT 2023 Medicom Conference Report. It was organised as a hybrid meeting, a format that has been shown most useful for medical conferences. The EBMT Annual Meeting, now held in Paris, is a great event that transplanters look forward to. It offers the opportunity to get informed on all aspects of stem cell transplantation. Mostly clinical but also basic and translational topics were covered in a wonderful programme. From this years' EBMT, we selected a number of interesting abstracts that will most likely change your daily practice now or in the near future. The abstracts are summarised in a way that the information is easy to digest in a rather short time.

The emerging role of transplantation in a variety of haematological malignancies got a lot of attention. But also transplantation possibilities in benign haematological disorders like haemoglobinopathies were discussed. Maintenance treatment after transplantation is an emerging new field that receives ongoing interest and research. The further deciphering of the molecular basis of malignant diseases offers possibilities to further stratify patients for transplantation. Much attention was also paid to new strategies to prevent and treat graft-vs-host disease (GvHD).

Finally, CAR T was a major topic during this meeting showing rapid developments and progress in clinical utility in many haematological diseases. Unravelling the mechanisms of GvHD offered the possibility to investigate many new drugs in this area. Measurable residual disease becomes an important surrogate endpoint for outcomes in many haematological malignancies and helps to inform treatment.

You will find snapshots of all these new developments in this report. I can imagine that these are helpful in your daily practice and am certain that you will enjoy them.

Gert Ossenkoppele

Biography

Gert Ossenkoppele is appointed in 2003 as professor of Hematology at the VU University Medical Center in Amsterdam. He obtained his doctorate of medicine at that same University in 1977. He is board certified in Hematology and Internal medicine(1984). The title of his PhD thesis (1990) was: "Differentiation induction in AML". Gert Ossenkoppele has authored over 450 publications in peer-reviewed journals and is invited speaker at many national and international scientific meetings. His research interests is mainly translational and include the (stem cell) biology of AML, leukemic stem cell target discovery, immunotherapy and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML. He is PI of national and international clinical trials in myeloid malignancies. He is reviewer on a regular basis for many high impact hematological journals (Blood, Leukemia, Haematologica, JAMA Oncology, Lancet Oncology NEJM). He chairs the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and recently stepped down as vice-chair of the HOVON Executive Board. He is a lead participant of the AML Work package of the European LeukemiaNet(ELN) as well as a board member of the ELN foundation. He co-leads the AML WP of HARMONY. He rotated of as board member of the European Hematology Association and was very recently appointed as vice-chair of the EHA Educational Committee. He just rotated of as chair of the AML Scientific working group of EHA and is now a member of this group. He is member of the Global and EU steering committee of the AMLGlobalPortal an educational portal for hematologists. (www.amlglobalportal.com). He chairs the institutional DSMB of his University. He has now because of retirement an honorary position as hematologist at the Amsterdam University Medical center.

Conflict of Interest Statement:
Prof. Gert Ossenkoppele received research support from Novartis, J&J and BMS-Celgene. He functions as a consultant for J&J, Daiichi-Sanyko, BMS-Celgene, Servier, and Roche. Lastly, he is a member of the advisory boards of Novartis, Pfizer, Abbvie, J&J, Daiichi-Sanyko, BMS-Celgene, AGIOS, Amgen, Astellas, Roche, Jazz pharmaceuticals, and Merus.

Acute Leukaemia

Quizartinib plus chemotherapy improves OS in patients with AML undergoing ASCT

In patients with newly diagnosed acute myeloid leukaemia (AML) with FLT3 internal tandem duplication (ITD), the addition of quizartinib on top of standard induction and consolidation therapy improved overall survival (OS) in the phase 3 QuANTUM-First trial. Findings from a subset of patients who underwent allogeneic stem cell transplantation (ASCT) in first complete remission showed that quizartinib still resulted in significant OS improvement.

"The QuANTUM-First study (NCT02668653) is the first randomised trial examining the efficacy and safety of a specific *FLT3* inhibitor in patients with AML and *FLT3*-ITD receiving up to 3 years of maintenance therapy after standard high-dose cytarabine consolidation or ASCT in first complete remission," explained Prof. Radovan Vrhovac (University Hospital Centre Zagreb, Croatia) [1,2]. Participants with newly diagnosed *FLT3*-ITD AML between 18 and 75 years of age (n=539) were randomised 1:1 to additional quizartinib during induction, consolidation, and as maintenance, or to placebo. After a median follow-up of 39 months, the primary endpoint of OS was met (median OS 31.9 months vs 15.1 months; HR 0.78; 95% CI 0.62-0.98; P=0.032) [3]. Prof. Vrhovac presented the findings from a subset of patients who underwent ASCT in first complete remission.

In total, 157 participants underwent ASCT in first complete remission. Multivariate analysis in this subset of patients showed that treatment with quizartinib (HR 0.77; 95% CI 0.61–0.97; P=0.028), as well as ASCT in complete clinical remission (HR 0.42; 95% CI 0.30–0.60; P<0.0001) had a positive and significant impact on OS. Prof. Vrhovac commented that these results were significant irrespective of pre-ASCT MRD status.

In conclusion, quizartinib provided a clinically meaningful improvement in OS compared with standard induction and consolidation therapy alone in patients with newly diagnosed AML with FLT3-ITD, irrespective of whether patients were transplanted or not.

1. Schlenck RF, et al. Impact of allogeneic hematopoietic cell transplantation in first complete remission in addition to FLT3 inhibition with quizartinib in acute myeloid leukemia with FLT3-internal tandem duplication: Results from the QuANTUM-First Trial. OS01-04, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.
2. Erba HP, et a;. Lancet. 2023;401(10388):1571–1583.
3. Erba HP, et al. Hemasphere. 2022;6(S3):S100.

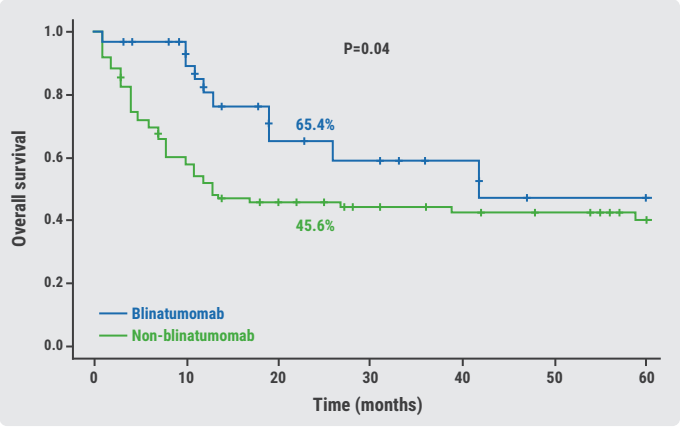
Blinatumomab may improve outcomes in patients with B-cell ALL undergoing ASCT

In a retrospective study, pre-transplantation blinatumomab was linked to better overall survival (OS) and reduced treatment-related mortality in patients with B-cell acute lymphoblastic leukaemia (ALL) undergoing allogeneic stem cell transplantation (ASCT). The authors emphasised that larger prospective trials are needed to confirm the results of the current retrospective study, which had a relatively small number of participants.

This retrospective study investigated the efficacy of pre-transplant blinatumomab in participants with B-cell ALL undergoing ASCT. Out of the 117 participants undergoing ASCT for B-cell ALL, 31 had received pre-transplant blinatumomab and 86 participants had not. Dr Ayman Sayyed (University of Toronto, Canada) presented the primary outcomes of OS and transplant-related mortality [1].

The median OS was 42 months in the blinatumomab group compared with 13 months in the non-blinatumomab group (HR 0.50; 95% CI 0.26–1.00; P=0.04; see Figure).

Figure: Overall survival blinatumomab versus no blinatumomab group [1]



Furthermore, a multivariate analysis showed that significant independent factors that positively influenced survival included blinatumomab (HR 0.48), total body irradiation (TBI)-based conditioning (HR 0.26), and paediatric-inspired induction protocol (HR 0.18). A mismatched donor was negatively associated with survival (HR 3.47). Considering transplant-related mortality, only 3.2% of the patients in the blinatumomab group had a transplant-related death compared with 43.0% of the patients in the non-blinatumomab group (HR 0.06; P=0.007).

The limitations of this retrospective study include that the blinatumomab and no-blinatumomab groups were not balanced with regard to patient and transplant characteristics. Further, the HCT regimen for nearly all patients in the blinatumomab group included T-cell depletion and PT-CY for GvHD prophylaxis, known to result in less severe acute GvHD, which may have contributed to the lower non-relapse mortality in the blinatumomab group.

"The effect of blinatumomab on OS and transplant-related mortality, confirmed by multivariate analysis, suggested that the reduction in transplant-related mortality is possibly related to a lower burden of treatment-related toxicity, experienced by patients who received fewer cytotoxic agents during induction therapy," argued Dr Sayyed. "Larger prospective trials are needed to further clarify the role of blinatumomab in the context of patients with B-cell ALL undergoing AHCL."

1. Sayyed A, et al. Pre-transplant blinatumomab improves outcomes in B-cell acute lymphoblastic leukemia patients who undergo allogeneic hematopoietic cell transplantation. OS06-05, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.

Is ASCT a reasonable option in patients with invasive aspergillosis?

Most patients with leukaemia and invasive aspergillosis (IA) undergoing allogeneic stem cell transplantation (ASCT) will benefit from this procedure. This was the main conclusion from a prospective study of the EBMT Infectious Diseases Working Party (IDWP). Thus, IA should not be considered an absolute contraindication for ASCT, according to the authors.

"IA is common during the treatment of acute leukaemia," said Prof. Olaf Penack (Charité University Hospital of Berlin, Germany) [1]. "Since anti-fungal management has improved in recent years, it is interesting to examine the influence of IA on health outcomes in a recent cohort of patients with acute leukaemia and IA undergoing ASCT." The current prospective study included 1,527 participants. The primary outcome was the 1-year non-relapse mortality.

The incidence of IA was 6.2% (n=95). A multivariate analysis demonstrated that the cumulative incidence of non-relapse mortality at 1-year post-ASCT was 16.9% in participants with IA and 11.4% in participants without IA (HR 1.9; 95% CI 1.12–3.28; P=0.02). Corresponding HRs for relapse-free survival and 1-year overall survival were 1.54 and 1.70, favouring the non-IA group over the IA group significantly.

"In total, 67% of patients with IA and 79% of patients without IA were alive at 1-year post-ASCT, displaying that IA is still a significant risk factor," interpreted Prof. Penack the findings. "More importantly, patients with IA have a high chance of surviving ASCT. Therefore, IA should no longer be considered as an absolute contraindication for ASCT," he concluded.

1. Penack O, et al. Influence of invasive aspergillosis during leukaemia treatment on survival after allogeneic stem cell transplantation: a prospective study of the EBMT infectious diseases working party. OS08-01, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23¬–26 April 2023, Paris, France.

Tacrolimus versus cyclosporine A in AML

In patients with acute myeloid leukaemia (AML) who are in first complete remission undergoing T-cell replete haematopoietic cell transplantation (HCT) with either haploidentical or unrelated donors, tacrolimus or cyclosporine A combined with post-transplantation cyclophosphamide (PTCy) and mycophenolate mofetil (MMF) resulted in similar overall survival (OS) and graft-versus-host disease (GvHD)-free, relapse-free survival (GRFS) outcomes. However, tacrolimus was associated with a decreased risk of acute GvHD compared with cyclosporine A in the subset of patients with haploidentical donors.

"In patients with AML who are in first complete remission undergoing T-cell replete HCT and PTCy, it is unknown whether the choice of calcineurin inhibitor influences outcomes," said Dr Gesine Bug (Goethe University Frankfurt, Germany) [1]. Therefore, Dr Bug and colleagues retrospectively compared GvHD prophylaxis cyclosporine A with tacrolimus, in combination with PTCy and MMF in a cohort of participants with AML in first complete remission (n=2,427). The main outcomes of the study were OS, the cumulative incidence

of relapse and relapse-free survival, and the cumulative incidence of acute and chronic GvHD and GRFS.

Participants in the cyclosporine A group (n=1,528) were more likely to have a haploidentical donor than participants in the tacrolimus group (n=899; 81% vs 67%; P<0.0001). Also, 31% of the participants in the cyclosporine A group received bone marrow compared with 16% of the participants in the tacrolimus group (P<0.0001). No difference was observed in OS between the 2 study groups, with 3-year OS rates of 66.3% and 64.5% (P=0.75). A multivariate analysis showed that within the subgroup of patients with haploidentical donors (n=1,844), acute GvHD was more common in the cyclosporine A arm than in the tacrolimus arm (HR 0.64; 95% CI 0.42–0.98).

"These results suggest that tacrolimus may be the preferred calcineurin inhibitor to combine with PTCy-based immunosuppression in patients with AML in first complete remission undergoing HCT with a haploidentical donor," concluded Dr Bug.

1. Bug G, et al. Use of cyclosporine A versus tacrolimus combined with post-transplantation cyclophosphamide for AML in first complete remission: A study from the acute leukemia working party (EBMT). OS01-06, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.

Promising novel target identified for AML

Vasoactive intestinal peptide (VIP) is an immunosuppressive peptide which is overexpressed in acute myeloid leukaemia (AML), and VIP receptor antagonist peptides have been associated with the induction of protective immunologic memory in mice with leukaemia and activated human T cells *in vitro*. According to the research team investigating this novel target in AML, the development of a longer-acting form of VIP receptor antagonist is underway.

"VIP is a neuropeptide that is known to be secreted by myeloid progenitor cells, nerves, and activated T cells, binding on receptors on dendritic cells and naïve T cells, leading to tolerogenic dendritic cells, and ultimately to regulatory T cells, which downregulate Th1 and upregulate Th2 polarisation," explained Prof. Edmund Waller (Emory University, GA, USA) [1]. "These regulatory T cells have been shown to inhibit activated T cells," added Prof. Waller. A research team looked at the possibility to target VIP in AML. "We know that VIP binds to surface receptors VPAC1 and VPAC2, which are present on the T cells of humans and mice," Prof. Waller continued.

The authors used *in silico* screening to map a library of alternative peptide sequences to identify peptide sequences with high binding affinity to human VPAC1 and VPAC2. Subsequently, the investigators selected the peptide sequences with potent antileukaemic activity in mice.

Various VIP receptor antagonists were associated with improved survival and delivered durable remissions in mice with leukaemia. Furthermore, higher dose intensities of VIP receptor antagonist therapies were linked to superior survival outcomes compared with lower dose intensities. "Mice that survived the initial leukaemic challenge after treatment with the VIP receptor antagonist were resistant to subsequent re-challenges with the same leukaemia," added Prof. Waller. Finally, VIP receptor antagonist peptides activated human T cells *in vitro*.

"VIP receptor antagonists enhance T-cell dependent anti-leukaemic effects," said Prof. Waller. "A longer-acting form of VIP receptor antagonists is currently being developed."

1. Waller EK, et al. Novel immunotherapy for AML. OS21-03, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.

Multiple Myeloma

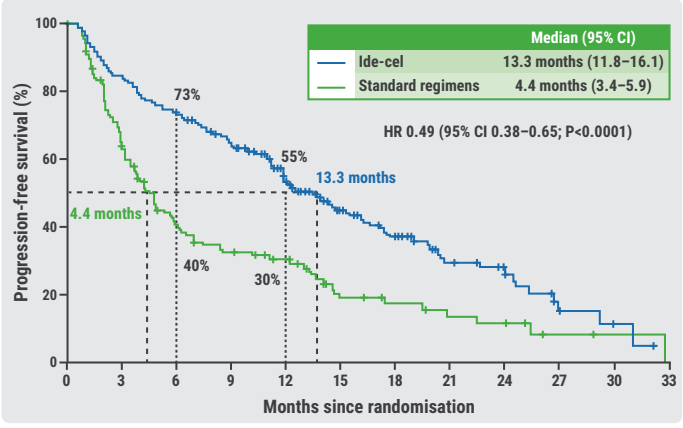
Ide-cel superior to standard therapies in triple-class exposed RRMM

Idecabtagene vicleucel (ide-cel) outperformed standard regimens in patients with triple-class exposed relapsed and refractory multiple myeloma (RRMM). The results of the phase 3 KarMMa-3 study supported the use of ide-cel in this hard-to-treat population.

"Novel therapies are needed in earlier lines of treatment for patients with MM," stated Dr Paula Rodríguez-Otero (Clinica Universidad de Navarra, Spain) [1,2]. "The B-cell maturation antigen [BCMA]-directed CAR T-cell therapy ide-cel has displayed promising efficacy in a heavily pre-treated population of patients with RRMM, and we aimed to study this agent in earlier lines of therapy" [1,3]. The phase 3 KarMMa-3 trial (NCT03651128) compared ide-cel with standard treatment regimens in patients with triple-class exposed RRMM who had received 2 to 4 prior lines of therapy and were refractory to the last treatment regimen (n=386). The participants were randomised 2:1 to ide-cel or standard treatment. Progression-free survival (PFS) was the primary endpoint.

The median PFS was significantly longer in patients who received ide-cel compared with those who received a standard regimen (13.3 months vs 4.4 months; HR 0.49; 95% CI 0.38–0.65; P<0.0001; see Figure). "This result was consistent across subgroups, including older patients, those with a high tumour burden, and patients with high-risk cytogenetic abnormalities," added Dr Rodríguez-Otero. Furthermore, the overall response rates (71% vs 42%; OR 3.47; P<0.0001) and the median duration of response (14.8 months vs 9.7 months) were higher in the ide-cel arm than in the control arm. Dr Rodriguez-Otero mentioned that the overall survival data were not yet mature at the time of the analysis. Finally, the safety data were consistent with the ide-cel toxicity profile reported in previous studies [1,4].

Figure: PFS in the intention-to-treat population of the KarMMa-3 study [1]



CI, confidence interval; HR, hazard ratio; ide-cel, idecabtagene vicleucel; PFS, progression-free survival.

In conclusion, the findings of the KarMMa-3 trial support the use of ide-cel in patients with early-line relapse and triple-class exposed RRMM, but OS data should be awaited.

1. Rodriguez-Otero P, et al. Idecabtagene vicleucel versus standard regimens in patients with triple-class-exposed relapsed and refractory multiple myeloma: KarMMa-3, a phase 3 randomized controlled trial. GS02-10, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.
2. Rodríguez-Otero P, et al. N Engl J Med 2023;388:1002–1014.
3. Munshi NC, et al. N Engl J Med 2021;384:705–716.
4. Raje N, et al. N Engl J Med 2019;380:1726–1737.

ASCT or CAR T cell as first-line therapy for MM?

Although autologous stem cell transplant (ASCT) is still the frontline therapy for patients with multiple myeloma (MM), CAR T-cell therapies have demonstrated high efficacy rates in later treatment lines, and emerging data suggest that perhaps it should be considered for earlier lines of treatment.

Prof. Salomon Manier (Lille University Hospital, France) compared the value of ASCT and CAR T-cell therapies for the treatment of patients with MM. "We do not have data from phase 3 trials comparing ASCT to CAR T-cell therapy in patients with MM," Prof. Manier stated [1]. "Therefore, we do not yet know which is the better option. We can, however, speculate on this topic using the currently available data."

ASCT has been shown to deliver an additional 1 to 2-year progression-free survival when added to a standard-of-care therapy [2–5]. The data does not demonstrate a benefit of ASCT on overall survival. "However, when we look at the IFM2009 trial, we can see that 76% of the patients who relapsed in the control arm received delayed ASCT, confounding the overall survival data," added Prof. Manier

[1,3]. Furthermore, additional ASCT is associated with higher minimal residual disease (MRD)-negativity rates (10^{-6}) than the standard triple therapy of lenalidomide, bortezomib, and dexamethasone (RVd) alone (29.8% vs 20.4%; P=0.01) [3]. Similarly, higher 1-year persistent MRD-negativity rates (10^{-5}) were reported for carfilzomib, lenalidomide, dexamethasone (KRd) plus ASCT than for KRd alone (90% vs 78%).

"What can we expect from CAR T-cell therapies in terms of MRD negativity?" asked Prof. Manier [1]. The phase 2 KarMMa trial, investigating idecabtagene vicleucel (ide-cel) in participants with MM in the late-stage setting, showed an MRD-negativity (10^{-5}) rate of 48% for participants who were treated with the recommended dose of ide-cel [6]. Also, in the phase 1b/2 CARTITUDE-1 trial, ciltacabtagene autoleucel (cilta-cel) displayed an MRD-negativity rate of 91.8% in participants with MM who received 6 prior lines of therapy and were evaluable for MRD [7]. The MRD-negativity rate was 58% when the complete study population was considered. "Then we have the DUAL FasT CAR-T cells, targeting BCMA and CD19," continued Prof. Manier. "A phase 2 study evaluating this option in a heavily pre-treated patient population showed that 100% of the participants who were evaluable for MRD (27 out of 28) reached MRD negativity" [1,8].

Prof. Manier commented that the results from these trials do not come from intention-to-treat populations but from patients who actually received CAR T-cell therapies. The KarMMa-3 trial (n=386) did provide results from an intention-to-treat population. The included participants had received 2 to 4 prior lines of therapy and were randomised 2:1 to ide-cel or a standard regimen, resulting in a clear progression-free survival benefit for participants who were treated with ide-cel (13.3 months vs 4.4 months; HR 0.49; P<0.0001) [9]. In total, 20% of the participants reached a complete response or better plus MRD negativity (10^{-5}). "Furthermore, emerging data is showing that early CAR T-cell therapy is likely to result in better responses than when this type of therapy is administered in later lines," said Prof. Manier [1,10,11].

The phase 3 CARTITUDE-6 trial (NCT05257083), comparing head-to-head in the frontline ASCT and CAR T-cell therapy following DRVd, will provide more insights. "Since a high tumour burden is a risk factor for severe cytokine release syndrome (CRS), the results of this trial may show us that frontline CAR T-cell therapy reduces the rate of severe CRS compared with administering CAR T-cell treatment in later lines of therapy," added Prof. Manier.

1. Manier S. CAR-T versus ASCT in Myeloma. JS03-2, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.
2. Attal M, et al. N Engl J Med 1996;335(2):91–97.
3. Attal M, et al. N Engl J Med 2017;376:1311–1320.
4. Richardson PG, et al. N Engl J Med 2022;387:132–147.
5. Gay F, et al. Lancet Oncol. 2021;22(12):1705–1720.
6. Raje NS, et al. Abstract 635, ASH 2020, 05–08 December.
7. Usmani SZ, et al. J. Clin. Oncol. 2021;39(15)_suppl:8005–8005.
8. Du J, et al. J. Clin. Oncol. 2022; 40(16)_suppl:8005–8005.
9. Rodríguez-Otero P, et al. N Engl J Med 2023;388:1002–1014.
10. Cohen AD, et al. JCI. 2019;129(6):2210–2221.
11. Garfall AL, et al. Blood Adv. 2019;3(19):2812–2815.

DETERMINATION: Does one size fit all in multiple myeloma?

A subgroup analysis of the DETERMINATION trial, comparing lenalidomide, bortezomib, and dexamethasone (RVd) alone with RVd plus autologous stem cell transplant (ASCT) in patients with newly diagnosed multiple myeloma (MM), suggested that one size does not fit all. According to the authors, further studies are warranted to personalise therapy for patients.

The DETERMINATION trial (NCT01208662) randomised 729 newly diagnosed patients with MM (Black/African American 18.8%; White 76.4%) 1:1 to RVd alone or RVd plus ASCT [1]. The primary outcome of progression-free survival (PFS) showed that patients in the RVd plus ASCT arm had a significant benefit over patients in the control arm, with a median PFS of 67.5 months versus 46.2 months (HR 1.53; P<0.0001) [2]. "MM is a heterogeneous disease and newly diagnosed patients with MM are diverse," Dr Hani Hassoun (Memorial Sloan Kettering Cancer Center, NY, USA) pointed out. "Therefore, we need to investigate whether one size fits all." A subgroup analysis for PFS was performed to gain insights into this matter.

"Although most subgroups appeared to benefit from a transplant, some subgroups need to be considered," continued Dr Hassoun. The benefit of transplant may be more apparent in White participants (HR 1.67; 95% CI 1.29–2.15) compared with Black/African American participants (HR 1.07; 95% CI 0.61–1.89). Also, those with a BMI <25 (HR 2.60; 95% CI 1.56–4.31) displayed a more pronounced advantage of transplant than those with a BMI between 25 and 30 (HR 1.24; 95% CI 0.86–1.80) or those with a BMI ≥30 (HR 1.41; 95% CI 0.98–0.02). Finally, patients with revised MM international staging system (R-ISS) III (HR 0.96; 95% CI 0.43–2.13) may have less benefit from transplant than those with R-ISS II (HR 1.63; 95% CI 1.22–2.19) or R-ISS I (HR 1.38; 95% CI 0.90–2.12). However, Dr Hassoun mentioned that

R-ISS status and race were independent prognostic factors for PFS, favouring R-ISS I over R-ISS II and III in both arms and favouring Black over White in the RVd alone arm.

"We observed that there may be a differential impact of baseline prognostic factors on the treatment that is applied, potentially indicating differences in myeloma pathobiology within certain subgroups," explained Dr Hassoun. "These data could help to differentiate patients who would benefit from ASCT, especially in the context of newer immunotherapies," he decided.

1. Hassoun H, et al. Response rates and outcomes in newly diagnosed multiple myeloma patient subgroups receiving RVd + ASCT plus lenalidomide maintenance until progression in the phase 3 DETERMINATION trial. OS02-08, European Society for Blood and Marrow Transplantation (EBMT) 49th Annual Meeting, 23–26 April 2023, Paris, France.
2. Richardson PG, et al. N Engl J Med 2022;387:132–147.

Graft-Versus-Host Disease

New options to treat steroid-refractory chronic GvHD

Chronic graft-versus-host disease (GvHD) is the most common long-term adversity after allogeneic haematopoietic cell transplantation (HCT). Although clinicians are still struggling with steroid-refractory chronic GvHD, novel agents have delivered promising efficacy results in recent years. Prof. Mohamad Mohty (Sorbonne University, France) discussed the emerging options to treat patients with chronic GvHD in whom systemic therapy had failed.

"The number of patients experiencing chronic GvHD has not dropped in recent years," said Prof. Mohty [1]. "The increased use of peripheral blood stem cells, the treatment of older patients, and the fact that we are treating more advanced disease are all risk factors for increasing the incidence of chronic GvHD [2]. The outcomes in patients with steroid-refractory GvDH are abysmal." Prof. Mohty added that steroid-refractoriness as well as steroid dependence and steroid intolerance are serious problems for patients [1,3].

Fortunately, there is a wide variety of upcoming drug candidates to treat chronic GvHD. "The use of corticosteroids has been declining, and novel agents are being administered more frequently," clarified Prof. Mohty [1,4]. "I would like to highlight some of the relevant trials," he continued. A study by Flowers et al. demonstrated that extracorporeal photopheresis (ECP) plus conventional therapy was associated with an increased cumulative incidence of complete response/partial response in skin compared with conventional therapy alone in patients with steroid-refractory or steroid-dependent chronic GvHD [5]. The most obvious responses were observed in cutaneous and mucosal manifestations.

"However, the largest improvements in the field of chronic GvHD have been made in the last 5 years, with the [FDA] approval of ibrutinib, belumosudil, and ruxolitinib," emphasised Prof. Mohty. In a phase 2 trial (n=42), ibrutinib displayed an overall response rate of 67% and a complete response rate of 21% in adult patients with chronic GvDH who failed 1 or more lines of systemic therapy [6]. In addition, 24% of the patients had a clinically meaningful improvement on the Lee chronic GvHD Symptom Scale, and 71% of the responders demonstrated a sustained response of ≥20 weeks.

Also in a phase 2 trial, belumosudil showed an overall response rate of 76% in patients ≥12 years of age with chronic GvHD who had failed at least 2 prior lines of systemic therapy [7]. The complete response rate was relatively low, at 5%. "On the other hand, the responses were relatively quick, with a median time to first response of 1.8 months," said Prof. Mohty. Moreover, this agent displayed efficacy across all organ systems. "Finally, this drug appears to be relatively safe," mentioned Prof. Mohty.

In a phase 3 trial, ruxolitinib demonstrated an overall response rate of 76% in patients ≥12 years of age with chronic GvHD who had failed one or 2 lines of systemic therapy [8]. This was significantly better than the 'best-available-therapy' control arm. Furthermore, the failure-free survival was increased in patients on ruxolitinib compared with those receiving the best available therapy (not reached vs 5.7 months; HR 0.37;

P<0.0001), and a significant improvement was seen on the Lee chronic GVHD Symptom Scale in patients who were treated with ruxolitinib. "Safety issues that are commonly seen with JAK inhibitors, such as cytopaenias and infections were quite manageable in this trial," added Prof. Mohty.

"Beyond ibrutinib, ruxolitinib, and belumosudil, there are many other agents, such as low-dose IL-2, mTOR inhibitors, low-dose methotrexate, mycophenolate mofetil, and rituximab may be of use in these patients as well," Prof. Mohty said. "Although there is still much work to be done, based on the new drugs that have become available for our patients with steroid-refractory chronic GvHD, I am optimistic," concluded Prof. Mohty.

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New developments in steroid-refractory acute GvHD

A large unmet need exists in managing patients with refractory acute graft-versus-host disease (GvHD). Prof. Ronjon Chakraverty (University of Oxford, UK) talked about his perspective on this topic and discussed ongoing trials that may provide better outcomes for these patients.

"We still don't know how to treat steroid-refractory acute GvHD, and we need to address this huge unmet need," stressed Prof. Chakraverty [1]. The Janus kinase (JAK)1/JAK2 inhibitor ruxolitinib has presented itself as the new standard-of-care for treatment-resistant acute GvHD in the REACH-2 trial, displaying a 28-day response rate of 62.3% compared with 39.4% for participants who were randomised to the control arm (P<0.001) [2]. "However, at the time of the trial closure, approximately 50% of the patients had died," said Prof. Chakraverty. "Currently, trials will probably be looking not only at corticosteroid-refractory disease but also at ruxolitinib-refractory acute GvHD" [1,3]. In addition, Prof. Chakraverty mentioned that biomarkers may be helpful in quickly identifying patients who are refractory to both ruxolitinib and corticosteroids [1,4].

What is the best treatment approach in 2023?

"Currently, the best approach for treating patients with steroid-refractory acute GvHD is enrolling them in clinical trials," said Prof. Chakraverty. He highlighted specific trials that are currently ongoing in this area.

Good biological evidence has emerged that ruxolitinib protects intestinal stem cells in the gut and skin [5]. "Therefore, it is a good idea to keep exploring JAK inhibitors for the treatment of this disease," argued Prof. Chakraverty. Currently, tofacitinib (NCT05112263) and itacitinib (NCT04070781) are being evaluated. When regeneration of epithelial cells is considered, there are ongoing trials assessing progenitors and niche factors, such as lithium carbonate (NCT00408681), growth factors and hormones, like pregnyl and apraglutide (NCT02525029; NCT05415410), immune cells and cytokines, such as IL-22 IgG2-Fc (or F-652) (NCT02406651), and microbial stimuli, like MaaT013 and healthy faeces (NCT04769895; ISRCTN14530574). Prof. Chakraverty specifically mentioned the preclincial STARGAZE trial, evaluating a glucagon-like peptide 2 for the repair of intestinal stem cells and Paneth cells in acute GvHD, and a phase 1 trial assessing faecal microbiota transplant (FMT) in patients with steroid-refractory acute GvHD [6,7]. This last study showed a switch to donor-like microbiota in responders.

"Finally, I would like to emphasise that the priority in clinical trial design is combining regenerative therapies with targeted immune suppression," concluded Prof. Chakraverty.

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Miscellaneous Topics

Long-term success for CD19 CAR T-cell therapy in CLL

CAR T-cell therapy may be a solution for a subset of patients with heavily pre-treated, high-risk, ibrutinib-intolerant, relapsed or refractory chronic lymphocytic leukaemia (RR CLL), as shown by the 80-month follow-up results of a phase 2 trial.

"Although a [previously published] phase 1/2 trial study showed promising efficacy data of CD19 CAR T-cell therapy in patients with RR CLL, the follow-up duration of this trial was limited to 1 year," said Dr Emily Liang (University of Washington, WA, USA) [1]. To assess the long-term outcomes, the participants of the current phase 2 trial were followed for a median duration of 79.6 months. The study included 55 patients with ibrutinib-intolerant RR CLL who received 1 of 3 dose levels of JCAR014 CAR T-cell therapy [2]. In total, 49 participants were infused.

The 28-day overall response rate was 70%. Similarly, 28-day minimal residual disease (MRD) negativity (10^{-4}) was achieved by 70% of the patients. Of the patients that reached MRD negativity by flow cytometry (10^{-4}), 62% even reached MRD negativity by next-generation sequencing (10^{-6}).

The median duration of response was 18.9 months, and the 6-year duration of response rate was 26%. The median duration of response was significantly longer in patients who had MRD negativity (10^{-4}) at day 28 compared with MRD-positive patients (27.1 months vs 1.8 months; $P_{log\text{-}rank}<0.001$). This difference was even larger in patients with next-generation sequencing MRD-negativity (53.4 months vs 7.8 months; $P_{log\text{-}rank}=0.004$). Finally, the 6-year progression-free survival and 6-year overall survival rates were 18% and 31%, respectively.

These findings indicate that CD19 CAR T-cell therapy could be a viable option in heavily pre-treated patients with ibrutinib-intolerant RR CLL. "After 6 years of follow-up, 6 patients remained progression-free, suggesting that CD19 CAR T-cell therapy may even be curative in a subset of patients," Dr Liang concluded.

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Can molecular data improve prognostication in MDS patients undergoing HSCT?

In the prognostication of patients with myelodysplastic syndromes (MDS) undergoing haematopoietic stem cell transplant (HSCT), findings from a large, international study showed that molecular data modestly improved the prediction of overall survival (OS).

The Molecular International Prognostic Scoring System for myelodysplastic syndromes (IPSS-M) added molecular parameters into the prognostication for MDS [1,2]. However, since only 9% of the patients in the cohort of the study by Bernard et al. underwent HSCT, the applicability of the IPSS-M in the context of transplantation is unclear. Dr Carmelo Gurnari (Cleveland Clinic, OH, USA & Tor Vergata University, Italy) and co-investigators conducted a real-world study among 416 participants with MDS to evaluate the value of IPSS-M in transplantated patient. In the study cohort, 36% of the participants underwent the transplant upfront, and in 85% of treated cases, hypomethylating agents were given as bridge therapy.

The Revised International Prognostic Scoring System (IPSS-R), which uses haematological and cytogenetic instead of molecular parameters, stratified participants according to risk: very low (6%), low (17%), intermediate (19%), high (26%), and very high (32%) risk. The calculated IPSS-M scores resulted in a significant redistribution of participants with respect to these risk categories: very low (27%), low (18%), moderately low (14%), moderately high (15%), high (10%), and very high (16%). Furthermore, the c-index for overall survival was 0.583 for the IPSS-M and 0.547 for the IPSS-R, suggesting that the IPSS-M is slightly better at predicting OS outcomes than the IPSS-R. The c-index of IPSS-M for OS was lower than the observed c-indexes in the study by Bernard et al. and comparable with existing specific HSCT MDS risk scores [3].

The authors concluded that molecular data adds value to the prognostication of patients with MDS undergoing HSCT. Dr Gurnari argued that the lower c-indexes that were reported in the current study, as compared with the original IPSS-M study by Bernard et al., point out that there are transplant-related factors to consider beyond disease-specific variables and molecular information.

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Next-generation cell therapies for cancer: CAR-NK cells

Dr Katy Rezvani (MD Anderson Cancer Center, TX, USA) discussed the latest research regarding the development of CAR-natural killer (NK) cell therapies for hard-to-treat cancers. Can CAR-NK cell therapies become safe and effective off-the-shelf products?

"CAR T-cell therapies have resulted in a paradigm shift in our thinking of cancer treatment," said Rezvani [1]. "However, the currently available CAR T-cell therapies are all autologous and are therefore time-consuming and costly to produce." Another issue with these therapies, according to Dr Rezvani, is limited access. To improve this situation, Dr Rezvani and co-investigators looked at the possibility of using a healthy allogeneic donor to manufacture CAR therapies and freeze doses of these cells so they can be available as an off-the-shelf product. "This would increase access and speed, and reduce costs," added Dr Rezvani.

The general challenges to the use of allogeneic donors for CAR therapy are the risk for graft-versus-host disease, limited persistence, the choice of cell type, and the choice of donors. The research group of Dr Rezvani chose to study NK cells for this purpose. "The main advantages of NK cells over T cells in the context of allogeneic CAR therapy is that NK cells do not cause GvHD, and that NK cells attack cancer cells by means of the introduced CAR and by innate receptors, whereas T cells may cause GvHD and only have the CAR-mediated mechanism of killing cancer cells," explained Dr Rezvani. Also, NK cells are not associated with cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). "Various allogeneic NK cell sources are being evaluated at the moment, including peripheral blood, cord blood, NK cell line, and induced pluripotent stem cells," continued Dr Rezvani.

Dr Rezvani 's research focussed on cord blood. A phase 1 study that was published in 2020 demonstrated a complete response in 7 out of 11 patients with CD19-positive lymphoid tumours who were treated with CAR-transduced NK cells, without the arise of CRS, neurotoxicity, or GvHD [2]. Furthermore, CAR NK cells were detectable at 12 months post-infusion, even though the CAR NK cells were HLA-mismatched with the recipients.

Dr Rezvani's research group is interested in the mechanisms of resistance that are associated with CAR-NK therapy. An *in vivo* study by Li et al. showed that CAR-NK cell trogocytosis drives relapse by downregulating target antigen on tumour cells, resulting in NK exhaustion and fratricide [3]. However, the investigators were able to demonstrate that an inhibitory CAR against an NK-specific antigen prevented fratricide and exhaustion mediated by the on-target off-tumour effect of the activating CAR.

Can CAR NK cells be applied beyond CD19-positive tumours?

Dr Rezvani then explained that the research group aimed to target non-CD19-positive tumours. "We hypothesised that pre-complexing NK cells with bispecific antibodies or FC-enhanced antibodies prior to infusion facilitates CAR-like responses by NK cells," she said. "Pre-activation of NK cells with cytokines could potentially enhance persistence by inducing a memory phenotype," she added. An *ex-vivo* study by Kerbauy et al. displayed that IL-12/15/18 pre-activated NK cells prior to expansion are associated with upregulation of genes related to the JAK-STAT pathway and interferon-γ response [4]. If these pre-activated NK cells were then loaded with a bispecific antibody, they were able to target CD16 and CD30 on cancer cells.

This concept was tested in a clinical trial (NCT04074746) in a heavily pre-treated population of 41 patients with Hodgkin lymphoma who failed on brentuximab. The 28-day response rate was 92.5%, with a 65% complete response rate. Among patients who were treated with the highest dose level of these pre-complexed NK cells, the response rate was even higher. Furthermore, no cases of CRS, ICANS, or GvHD were reported [5]. "However, the responses were transient," added Dr Rezvani. "The results that were presented at ASH 2022 were based on a 2-cycle regimen. We need to await the follow-up responses of

the 4-cycle regimen to see whether this prolonged therapy can increase the duration of responses." She clarified that it is not surprising that the persistence of these NK cells was limited, given the short lifespan of NK cells.

Furthermore, Dr Rezvani and colleagues tested 34 different CD70 targeting CAR-NK constructs, using the extracellular domain of CD27, since CD70 is a natural ligand for CD27. The most promising CD70 CAR-NK cells displayed excellent antitumour activity and safety in mice with Burkitt lymphoma or acute myeloid leukaemia (AML). Importantly, the research group found a cryopreservation method that led to similar results for frozen CD70 CAR-NK cells as for fresh cells. Currently, 2 clinical trials are running to test IL-12/15/18 pre-activated CAR-NK cells in human populations (i.e. NCT05703854; NCT05092451).

"We need to develop CARs that target more than 1 antigen, combine CAR engineering with bispecific antibody loading, use the knowledge of cytokine engineering and CRISPR gene editing, and combine novel CAR therapies with checkpoint inhibitors, immunomodulatory drugs, and radiotherapy to begin to address the unmet need in hard-to-treat cancers such as AML and solid tumours," Dr Rezvani concluded her presentation.

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Novel drugs and strategies around ASCT for Hodgkin lymphoma

In recent years, several developments have resulted in improved outcomes for patients with primary refractory or relapsed classic Hodgkin lymphoma (cHL) who are eligible for autologous stem cell transplantation (ASCT), including the introduction of new drugs in combination with salvage chemotherapy before (ASCT), and improved consolidation strategies after ASCT. Dr Anna Sureda (Catalan Institute of Oncology, Spain) discussed the latest updates in the field [1].

ASCT is the standard-of-care for patients with classical cHL who achieve a second complete remission, being primary refractory or having relapsed after a first line of therapy [2]. "It appears that we are autografting fewer patients in recent years, due to improved first-line therapies," stated Dr Sureda.

For example, the ECHELON-1 trial showed that the experimental regimen of brentuximab vedotin plus AVD chemotherapy outperformed ABVD in terms of modified progression-free survival (PFS) and overall survival (OS) in patients with stage III or IV cHL [3,4]. Another emerging option is to combine AVD chemotherapy with checkpoint inhibitors such as pembrolizumab, which appears to be beneficial for patients with untreated cHL [5].

"Despite these encouraging developments, we still see a population of predominantly young patients that need ASCT," noted Dr Sureda. A trial by Schmitz et al. showed that ASCT is the standard-of-care for patients with relapsed or primary refractory cHL [6]. However, this trial also displayed that approximately 50% relapsed after ASCT. "Can we improve the results of ASCT in patients with primary refractory or relapsed cHL?" asked Dr Sureda.

Improving the outcomes of ASCT

"We have used 2 strategies to improve the outcomes of ASCT," said Dr Sureda. The first strategy is to differentiate patients with respect to the expected disease response using imaging techniques, such as PET or metabolic tumour volume (MTV) assessments, prior to ASCT [7,8]. The second strategy is incorporating drugs in the salvage setting before ASCT, such as brentuximab vedotin, targeting CD30-positive cells, or the checkpoint inhibitors nivolumab and pembrolizumab [9–11].

Several phase 1 and 2 trials assessing the combination of brentuximab vedotin and salvage chemotherapy before ASCT have indicated that this strategy leads to excellent outcomes (see Figure). The benefit appears to be more pronounced in

Table: Outcomes of brentuximab vedotin plus salvage chemotherapy before ASCT [1]

Author, year	N of patients	Protocol	ORR %	mCR %	N of patients proceeding to auto-HCT	PFS	OS
Moscowitz, 2015	46	Sequential BV + Augmented ICE	80	76	44 (96%)	90% (24 mo)	95% (24 mo)
LaCasce A, 2018	55	BV + Bendamustine	92.5	74	40 (75%)	70% (24 mo)	95% (24 mo)
Garcia Sanz R, 2019	66	BV + ESHAP	94	70	62 (94%)	70% (18 mo)	90% (18 mo)
Kersten MJ, 2020	55	BV + DHAP	90	81	47 (90%)	74% (24 mo)	95% (24 mo)

ASCT, autologous stem cell transplantation; OS, overall survival; ORR, overall response rate; mCR, maintained complete response; PFS, progression-free survival.

relapsed patients compared with primary refractory patients [12]. "Whether brentuximab vedotin plus chemotherapy is superior to chemotherapy alone in the second line setting has not yet been demonstrated," said Dr Sureda.

Next, chemotherapy plus pembrolizumab resulted in an overall response rate of 100% and a complete response rate of 95% in 38 patients who were treated with this regimen in the second line, before ASCT [13]. After a median follow-up of 30 months, the progression-free survival was 96%. Also, Advani et al. showed that chemotherapy-free regimens may lead to good outcomes in the second-line treatment for patients with cHL [14].

Is consolidation with ASCT always needed?

"Another question I would like to address is: Do we need to consolidate all patients with ASCT?" Dr Sureda continued. "We do not have the answer at this point." However, clinical trials are investigating this issue. Patients with primary refractory or relapsed cHL in the phase 2b BRESELIBET trial (NCT04378647) received either chemotherapy plus brentuximab vedotin or chemotherapy alone. Patients that achieved a metabolic complete response (n=22) were not consolidated with ASCT but with brentuximab vedotin. Similarly, in the trial by Moskowitz et al., patients who reached a complete remission on chemotherapy plus pembrolizumab were consolidated with pembrolizumab instead of an ASCT [13]. "Data from these trials may give us some insights into this issue," added Dr Sureda.

The role of consolidation after ASCT

"We also know that some patients are more likely to relapse after ASCT than others," continued Dr Sureda. To decrease the relapse rate after ASCT, the phase 3 AETHERA trial randomised 329 high-risk patients who had received ASCT 1:1 to brentuximab vedotin consolidation therapy or to placebo [15]. The trial was positive, with a 43% reduction in the risk of relapse or progression for patients in the experimental arm compared with patients in the control arm. The long-term outcomes of this trial confirmed that consolidation with brentuximab vedotin after ASCT leads to better outcomes than placebo in high-risk patients [16]. "Emerging data showed that pembrolizumab may be a promising agent for consolidation after ASCT as well," added Dr Sudera [17]. Finally, the combination of brentuximab vedotin and nivolumab, as a consolidation strategy after ASCT, displayed an encouraging progression-free survival rate of 92% after 19 months of follow-up in a group of high-risk patients (n=59) [18].

"With these encouraging developments going on, hopefully, we will be able to find a subset of patients with cHL in whom we can omit consolidation with ASCT in the nearby future," Dr Sureda concluded her talk.

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Thalassaemia: Advances in conventional transplantation and gene therapy

Updates regarding gene therapy and conventional transplantations in patients with thalassaemia were discussed by Prof. Josu de la Fuente (Imperial College London, UK). His talk included the importance of age for transplant outcomes, the feasibility of haploidentical transplantation, and the rise of gene therapies.

"Thalassaemia is a complex systemic disorder," said Prof. de la Fuente at the start of his presentation [1]. "α/β globin-chain imbalance leads to ineffective erythropoiesis, iron overload, and anaemia, resulting in marrow expansion, bone disease, organ damage, gall stones, and other manifestations." Prof. de la Fuente stressed that there is still a need for better therapies to treat patients with thalassaemia.

Conventional transplantation

Transplantation improves the quality of life for patients with transfusion-dependent thalassaemia (TDT) in terms of role limitation, bodily pain, and emotional functioning, except for those who develop chronic graft-versus-host disease (GvHD) [2]. "Expanded ineffective haemopoiesis is a risk factor for graft failure in patients with thalassaemia," continued Prof. de la Fuente [1]. Strategies to deal with this situation are hyper-transfusions, suppression of endogenous haemopoiesis with hydroxycarbamide and azathioprine, or the addition of thiotepa, particularly in young patients [3].

Fludarabine and beyond

"Next, fludarabine-based regimens have enabled unrelated donor transplantation for patients with TDT," said Prof. de la Fuente [1,4]. Also, a recent sibling bone marrow transplantation study (n=58) showed that the addition of serotherapy to fludarabine, treosulfan, and thiotepa (FTT) led to a low graft failure rate (3.4%), a 5-year overall survival rate of 96.6%, a median time to neutrophil engraftment of 12 days, a median time to cessation of immunosuppression of 170 days, and an acute GvHD grade II-IV rate of 13.8% [1]. "Less than 2% of the patients needed any treatment beyond 18 months," added Prof. de la Fuente.

The importance of age

Subsequently, Prof. de la Fuente showed 2 studies that demonstrated that age is the most important indicator for bone marrow transplantation outcomes, with the best results observed in patients up to 13 years of age [5]. "Thus, transplantation should be part of the treatment algorithm at an early point, probably before the age of 6 years," emphasised Prof. de la Fuente [1,6].

Post-transplantation cyclophosphamide

Importantly, graft failure rate and mortality are somewhat higher in mismatched donors [6,7]. The administration of post-transplantation cyclophosphamide (PTCy) may address this issue. This strategy enables reduced intensity conditioning (RIC) haploidentical transplantation and long-term engraftment in patients with thalassaemia [8]. Furthermore, pharmacologic pretransplant immunosuppression (PTIS) and abatacept reduce graft failure and improve the outcomes in mismatched patients receiving PTCy [9,10].

Gene therapies

"An alternative solution for obtaining a cure for patients with TDT is the use of corrected autologous cells by means of gene addition or gene editing strategies," explained Prof. de la Fuente. Treatment with betibeglogene autotemcel (beti-cel) in patients with thalassaemia did not lead to treatment-related adverse events 2 years post-infusion or vector-derived replication of the competent lentivirus. Also, 90% of the patients who have completed the phase 3 LTF-303 trial (n=10) achieved transfusion independence after a median follow-up of 26.1 months [11].

Finally, all patients with thalassaemia who were infused with the gene-editing therapy exa-cel (n=44) achieved neutrophil engraftment and platelet engraftment, in a median time of 29.0 and 43.5 months, respectively. Also, 42 out of 44 treated patients are transfusion-free, with durations between 0.8 and 36.2 months [12]. "The safety profile of exa-cel is consistent with that of busulfan myeloablation and autologous HSCT," added Prof. de la Fuente.

In conclusion, age is the most important determinant in transplant outcomes, indicating that early transplantation is crucial in patients with thalassaemia. Also, transplantation with unrelated donors and siblings lead to equal long-term outcomes in most patients. Next, haploidentical transplantation is feasible, addressing poor donor availability. Finally, strategies are emerging where a corrected form of a patient's stem cells may offer a solution for their disease.

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