# New Approaches to Allogeneic Hematopoietic Cell Transplantation

Cemaleddin Ozturk and Sinem Civriz Bozdag

*Department of Hematology, Ankara University Faculty of Medicine, Ankara, Turkey*

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**Corresponding Author:** Cemaleddin Ozturk, MD,

Department of Hematology Ankara University

Balkiraz Mah. Mamak Cd. No:12, 06620 Mamak/Ankara TURKEY

**E:** cemaleddinozturk@gmail.com **Twitter:** https://twitter.com/cemaleddinoztrk

**Linkedin:** https://www.linkedin.com/in/cemaleddin-%C3%B6zt%C3%BCrk-58715350/

ORCİD: 0000-0003-1591-6575

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**Abstract**

Allogeneic hematopoietic cell transplantation is a potentially curative therapeutic option for all hematologic malignancies. It is a double-edged sword that may result in significant mortality and morbidity. In recent years, there are groundbreaking advances in more availability of stem cell sources, emerging strategies for choosing the best donor, graft versus host disease (GVHD) prevention and treatment strategies as well as supportive care. Ultra-high resolution (UHR) using next-generation sequencing technology has been introduced to get more information that is sensitive on HLA typing possible to access the best-matched donors. Functional HLA matching with TCE3 and TCE4 and a scoring system named by "delta functional distance" (ΔFD) may help to GVL-GVHD counterbalance to the GVL direction. More effective GVHD prophylaxis (post-transplant cyclophosphamide and ATG) make it possible to reach broader donor diversity in terms of unrelated and haploidentical setting. Ex-vivo stem cell expansion with numerous small molecules (stem regenin 1, TAT-BMI1, nicotinamide, valproic acid) can improve engraftment and immune reconstitution rates in UCBT. Ruxolitinib, ibrutinib, vedolizumab, alpha-1 antitrypsin (AAT) and, mesenchymal stromal cells have promising results in the treatment of acute and chronic GVHD settings. Letermovir and maribavir have also encouraging results in CMV reactivation prophylaxis. This article summarizes the current state of art and paradigm shifts in allo-HCT.

**Keywords:** Allogeneic hematopoietic cell transplantation, GVHD, HLA typing, conditioning regimen, stem cell source



## 1) Introduction:

Allogeneic hematopoietic cell transplantation (Allo-HCT) has a bi-faceted role in the treatment of hematopoietic malignancies. Firstly, Allo-HCT gives a high dose chemotherapy chance to reduce the leukemic burden, and then graft originated NK and T cells inaugurate adoptive immunotherapy effect against leukemic cells via tumor-specific antigens (TSA), tumor-associated antigens (TAA), as well as minor histocompatibility antigens (miHA).[1-6] Allo-HCT plays the main role via graft versus leukemia (GVL) effect on residual leukemic cells.[7-9] The GVL effect can clinically be observed after donor lymphocyte infusions. In CML, approximately 70%-90% of the patients can achieve complete remission after DLI infusion.[10,11] Although, GVL effect is mainly potent in CML and acute myeloid leukemia (AML), the beneficial effect of GVL is restricted with GVHD. [11-14] Although Truitt et al. show a method to promote the GVL effect without triggering GVHD in an animal study, it is extremely intricate to drive the immune reactions to the GVL direction rather than the GVHD direction.[15] The state of art in allogeneic stem transplantation is based on balancing the graft versus host and the graft versus leukemia effect. Selecting the best donor, the wise use of the immunosuppressive drugs for graft versus host disease prevention and treatment, rapid engraftment, minimal toxicity with individualized conditioning regimens and supportive care are the fundamental elements to achieve this objective. In the last decade, with significant progress, allo-HCT has become a rational and curative option more than ever.[16,17] In this review, our purpose is to summarize the recent advances in allo-HCT.



## 2) Changing from Human Leucocyte Antigen (HLA) antigens analysis to functional HLA allele matching:

Identification of HLA antigens to find a matched donor is the major and initial step to perform an allo-HCT. HLA-dependent interactions between lymphocytes and antigen-presenting cells play a fundamental role in bidirectional graft-host interplays.[18] This relationship may lead to either graft rejection or graft versus host disease. The traditional low-resolution method was serological analysis to identify HLA proteins using antigen-specific anti-sera. Before two decades, HLA typing evolved from serological analysis to HLA polymorphism assays. Sequence-specific oligonucleotide (SSO) and sequence-specific polymerase chain reaction (SSP-PCR) methods are introduced which provide deeper details of amino acid differences.[19,20] Currently, Sanger sequencing method is accepted as a gold standard for HLA polymorphism analysis with the advantage of high-resolution tissue typing.[21] Although Sanger sequencing and sequence-specific oligonucletoide (SSO) methods are the elemental methods for HLA typing, next-generation techniques (NGS) have emerged in recent years which provide more sensitive, faster, and cost-effective information on HLA typing.[22-27] HLA typing with nanopore sequencing also offers higher and accurate throughputs in a faster manner than main NGS methods such as Ion Torrent and MiSeq.[28] RNA sequencing is another method, which can be used for HLA typing.[27] This method supplies precise HLA typing results as well as killer immunoglobulin-like receptors (KIR) mismatch which may prevent relapse after allo-HCT.[29,30]

An 8/8 match for HLA A-B-C-DR locus has been preferred for related donors. Only one-third of the patients may have a fully matched sibling donor.[31] Therefore, clinicians refer to alternative donor sources such as matched unrelated (URD), haploidentical or umbilical cord blood donors.

National Bone Marrow Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR) recommend DNA-based methods at high resolution for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLADPB1 loci. HLA-DQB1, HLA-DRB3/4/5, HLADQA1, and HLA-DPA1 typing underlined as a helpful strategy to avoid graft failure risk via determining possible HLA-sensitized patient but not for routine testing for donor selections even if no impact on survival has been shown.[32,33] HLA mismatches trigger T cell alloreactivity in distinct levels determined by T-cell-epitope (TCE) mismatching.[34] In the last years, in-silico modelings are developed to test functional HLA-DPB1 matching such as T-cell epitope (TCE) analysis (TCE3 and TCE4) and a scoring system named by "delta functional distance" (ΔFD) derived from DPB1 T-Cell epitope algorithm.[35] These attempts are the first steps to achieve a significant breakthrough in the HLA typing paradigm.

Moreover, the functional matching of HLA may contribute significantly to counterbalance between GVL and GVHD. Consistently, using these methods may improve outcomes of allo-HCT in terms of overall survival (OS), non-relapse mortality (NRM), GVHD and relapse-free survival (GRFS), and risk of relapse.[35-38]

### 3) Which donor type is better unrelated, cord blood or haploidentical donor?

Despite all the advances in allo-HCT from alternative donor sources, HLA-identical sibling donor transplantation is considered as a gold standard in clinical practice for allo-HCT.[39-42] In the USA, the probability of 10/10 HLA matched sibling donors ranges from 13% to 51%.[43,44] Sibling match

probability is 1.5 times lower in adults younger than 44-year-old compared to the older ones.[43,44] In this regard, finding an alternative donor is indispensable. In a prospective study, Yakoup-Agha et al. shows URD HCT has comparable outcomes with MSD HCT in terms of OS and NRM. [45] There are also several encouraging studies with retrospective analysis to substantiate a place for URD HCT comparing to MSD HCT.[46-48] Recently, URD allo-HCT rates begin to lose its acceleration, and haploidentical donor HCT takes its place.[49,50] Access to an unrelated donor needs more time, endeavor, and funds.[51,52] Donor search costs and transportation expenditure of cell product, increased use of anti-thymocyte globulin (ATG) and defibrotide raise the cost of allo-HCT from unrelated donor exponentially. Donor volunteering, rapid availability of cell products in case of necessity during and after transplantation are the advantages of haploidentical transplantation.

More effective GVHD prophylaxis (post-transplant cyclophosphamide, ATG) and success in the selection of the best haploidentical donors make it more preferable in recent years. Although there is no randomized, controlled, prospective trial to examine, haploidentical HCT has comparable outcomes with URD HCT, UCBT, and even with MSD HCT in a retrospective cohort study in acute myeloblastic leukemia patients (AML).[53,54] Even though, haploidentical donors is not the first-line donor source for lymphomas, haploidentical transplantation with post-transplantation cyclophosphamide has been shown to result in similar outcomes with URD HCT and MSD HCT in Hodgkin lymphoma (HL).[55,56] For the thalassemia patients, the availability of a related donor is relatively low due to donor candidate may suffer the same disease. Allo-HCT from alternative donors such as MUD and haploidentical donor become more available

with each passing day.[57,58] Haploidentical HCT has also a grooving evidence body in severe aplastic anemia (SAA).[59-61] In a meta-analysis, performed by EBMT working party, demonstrate that haploidentical HCT can be a feasible option for SAA with acceptable engraftment success (engraftment rate 97.3%, 95% CI, 95.9–98.7) and relatively reduced complications (annual TRM rate: 6.7%, 95% CI, 4.0-9.4).[62] Although in recent years, chimeric antigen receptor T cell (CAR-T) therapies provide promising results in non-Hodgkin lymphoma (NHL), it is not plausible to say allo-HCT supersede by CAR-T cell therapy.[63,64] The role of haploidentical HCT is scarce in NHL patients compared to AML and HL. Dreger et al. demonstrated that post-transplant cyclophosphamide (PT-Cy) based unmanipulated haploidentical HCT in diffuse large B cell lymphoma (DLBCL) may have similar outcomes with MSD and MUD in terms of OS.[65] Kanate et al. also showed that PT-Cy based haploidentical HCT in NHL has comparable OS and NRM outcomes in addition to lower chronic GVHD (cGVHD) rates.[66] Recently, Dreger et al. conducted a large-scale retrospective analysis to compare haploidentical HCT with URD HCT and MDS HCT in DLBCL. There is no significant difference between the groups in terms of OS, NRM, and PFS but a lower incidence of cGVHD was seen in the haploidentical HCT group.[65]

Unrelated cord blood transplantation (UCBT) can be an alternative donor source in case of URD unavailability. Although the number of UCBT has decreased in recent years, it has pros and cons.[49,67] No need for HLA full match donor, availability for rare HLA types, no need to perform harvest, lower GVHD rates even in higher HLA mismatch are the advantages of cord blood. [31,68,69] Whereas, an increase in graft failure and delay in immune reconstitution as a result of a low number of $CD34^+$ counts especially for adult patients is one of the major concerns for UCBT.

Moreover, post-thaw stem cell counts can be lowered with the range of 1-25%.[70] Novel techniques are tested for improving engraftment and immune reconstitution in UCBT. UCB ex-vivo stem cell expansion with numerous small molecules (stem regenin 1, TAT-BMI1, nicotinamide, valproic acid, sitagliptin) have been introduced.[71-75] Moreover, hypoxia culturing, co-culture with mesenchymal stem cells, co-infusion with mesenchymal stem cell, double UCBT, co-infusion with the third party selected $CD34^+$ haploidentical stem cells are the other techniques for enhancing outcomes of UCBT.[76-79] However, further clinical confirmatory trials have to be performed for these promising stem cell expansion methods.

Due to the lack of randomized controlled trials comparing haploidentical HCT, URDT, and UCBT, local factors and the experience of the transplant centers mostly come to the fore in the preference of donor sources.



**4) Which conditioning regimen should be preferred? Which one to whom?**

The key determinant factors while choosing the conditioning regimens are the type and state of the disease, as well as the patient's comorbidities. Although, myeloablative (MAC) regimens have been preferred in younger and fit patients, reduced-intensity conditioning has been introduced for elderly and unfit patients with comorbidities. The consideration of the GVL effect of the allo-HCT has been constituted the rational basis of the reduced-intensity conditioning regimens (RIC).[80] The optimal conditioning regimen for patients older than 50 years remains controversial due to the lack of prospective randomized controlled studies.[81,82]

In young AML and myelodysplastic syndrome (MDS) patients, MAC regimens have been compared with RIC regimens. A phase III randomized controlled study showed better but not statistically significant OS at 18 months with MAC comparing to RIC (77.5 versus 67.7%, respectively p=0.07). Higher relapse rates are observed in RIC (67.8% and 47.3% respectively, p< 0.01). TRM is observed 15.8% (n=22) in MAC group, and 4.4% (n=8) in RIC group (p=0.02). [83] In another study, RIC and MAC regimens showed no significant differences in terms of OS (31% versus 24% respectively, p=0.10), 10 years NRM (16% versus 26%, respectively p=0.10), and 10 years disease-free survival (DFS) (55% versus 43%, respectively, p=0.19) in patients with intermediate and high-risk AML patients between 18-60 years.[84] In elderly AML patients, long term promising outcomes with more widely used regimens like fludarabine, busulphan has been shown previously. Recent data showed also more favorable outcomes in terms of progression-free survival (PFS) and GRFS comparing with Flu-Mel100 than Flu-Mel140, Flu-Bu4 (AUC>5000), Flu-Bu4 (AUC >4000) (with or without clofarabine). NRM at 3 years' data are 19%, 39%, 35%, and 21% (P =0 .06), and 3-year relapse rates are 32%, 32%, 30%, and 55% (P=0.003) respectively.[85] In a study that compares TBI based and busulphan based conditioning in AML shows no significant difference between groups in terms of the 2-year OS (64% versus 84%, p=0.73), PFS (52% versus 53%, p=0.96), RFS (76% versus 84%, p=0.95), NRM (27% versus 47%, p=0.56).[86] Clift et al. compares Bu/Cy and Cy/TBI combinations as a conditioning regimen in AML.[87] They show no difference between study arms in terms of OS, PFS, and NRM. In recent years, a considerable body of literature has grown up around the topic of minimal or measurable residual disease (MRD) which can be determined with multi-parametric flow

cytometry (MFC), PCR, or next generation sequencing techniques (NGS) as well. Mostly, it is not available to perform molecular MRD analysis for 60% of the patients due to a lack of a proper molecular marker for the RT-PCR technique.[88] To handle this limitation, NGS techniques can be used to provide a proper mutation to MRD follow-up for the 93% of AML patients.[89] The patients who have complete remission (CR) morphologically after AML treatment but ongoing MRD positivity before the allo-HCT, has lower OS and PFS outcomes comparing with the patients which achieved MRD negativity.[90,91] MRD assessment before transplantation can also shed out light on the decision of the allo-HCT in terms of which patients may benefit from the allo-HCT. Relatively, the GIMEMA AML1310 study is carried out to examine the clinical outcome of the risk-adapted post-remission therapy based on MRD assessment with PCR and MFC. In this study, MRD driven transplantation decision equalize the OS and PFS outcomes in MRD positive and negative AML patients with intermediate-risk characteristics.[92] Shah et al conducted a study to examine the MRD analysis after allo-HCT in AML patients. The study shows detection of MRD positivity in the early post-transplantation phase portends a higher relapse-risk. [93] Although the allo-HCT is a curative option for AML, the relapse incidence, and mortality rates remain high and this makes it reasonable to scientific seek for optimal post-transplant maintenance approach. Relaza-2 study is a phase II, single-arm study to set out to clarify the outcomes of azacitidine maintenance on MDS or AML patients with MRD positivity after allo-HCT or conventional chemotherapy. In this study, 58% (95% CI 44–72) of the patients who MRD positive, were relapse-free with azacitidine maintenance ($p<0,0001$).[94] In another major study, SORMAIN, which set out to examine the outcomes of sorafenib maintenance after allo-HCT in FLT-3 positive AML patients *w/wo* MRD positivity, show sorafenib maintenance

significantly reduced the risk or death and relapse (HR: 0.39, 95% CI, 0.18 to 0.85).[95] Relatively, Schlenk et al. demonstrate that single-agent maintenance of midostaurin in patients with FLT-3 positive AML after allo-HCT is safe and feasible. In this study, starting the midostaurin maintenance at day 100 after transplant has better EFS and OS outcomes comparing to within 100 days after transplant group.[96] An ongoing phase III randomized, placebo-controlled multicenter study is being conducted to test the outcomes of gilteritinib maintenance after allo-HCT in FLT-3 positive AML patients, the results are not published yet (NCT02997202).[97]

RIC regimens also can be feasible in older ALL patients. Mothy et al. show in a retrospective study, the type of conditioning regimen (MAC versus RIC) is not found in a relationship with leukemia-free survival (p = .23, HR = 0.84).[98] Marks et al. compares full-intensity and reduced-intensity conditioning in older ALL patients.[99] They show the intensity of the conditioning regimens does not affect outcomes of TRM (p=0.92) and relapse risk (p=0.14). Although total body irradiation (TBI) has been accepted as the key component of the conditioning regimens in acute lymphoblastic leukemia (ALL), rather than AML, acute and delayed toxicity of TBI remains as a substantial challenge. CIBMTR data showed a higher relapse rate (%38 versus %27 respectively, p=0.007) but similar survival rates (57% versus 53%, respectively, p=0.35) with busulphan based conditioning regimens in comparison with TBI based regimens in acute lymphocytic leukemia.[100] In a Korean study, TBI based conditioning regimens show favorable outcomes in young adults independently of acute leukemia subtype (p= .005).[101] Especially in patients younger than 40 years, TBI provides better 5-year OS (55.1%, p = 0.023) and DFS (48.6%, p = 0.020) outcomes than busulphan based conditioning regimens.[102] EBMT Acute

Leukemia Working Party showed the combination of TBI with etoposide as effective as combination with cyclophosphamide (HR: 0.62, p=0.04).[103] In a Japan retrospective analysis, iv BU/Cy has comparable outcomes with TBI based regimens in ALL.[104] Reduced-intensity conditioning regimens in ALL have been increased in recent years and mostly formed from chemotherapeutics only.[105] Up to now, there has been growing solid and convincing evidence to substantiate MRD-guided allo-HCT decision-making modality. Recent studies confirm that allo-HCT provides clinical benefit in terms of relapse risk and survival in Ph(-) and Ph(+) ALL patients who have ongoing MRD positivity after induction chemotherapy.[106,107] Dhedin et al. demonstrate that allo-HCT benefitted relapse-free survival Ph (-) B-ALL patients who have post-induction MRD positivity.[108] In a retrospective Chinese study claims that pre-transplantation MRD positivity results in higher cumulative relapse incidence (26.1% vs. 12.1%, *P* = 0.009) but NRM, OS, and LFS outcomes were comparable with MRD negativity which obtained before allo-HCT in Ph(+) ALL patients.[109] Although MRD is a broadly accepted key prognosticator in B-ALL, it is understudied in T-ALL. Modvig et al. analyzed the effect of flow cytometry-based MRD assessment on the outcomes of T-ALL patients. They show the patient who has FCM-MRD ≥ $10^{-3}$ [at] the end of the induction has a higher hazard ratio for relapse compared to FCM-MRD ≤ $10^{-3}$.[107]

Allo-HCT can be a curative treatment option in lymphomas on the basis of the GVL effect. The long-term outcomes of RIC and MAC regimens in diffuse large B cell lymphoma (DLBCL) are similar as a result of higher 5-year NRM (56% vs 47% P =0.007) in MAC and 5-year PFS in RIC (26% vs 38% p=0.031) regimens. There is no difference at 1, 3 and 5-year OS outcomes

between MAC and RIC at (1 year: 38% vs 46% vs 45%; 3 years: 21% vs 27% vs 29%; 5 years: 18% vs 20% vs 26%).[110] In RIC regimens, the importance of lymphoma histology on the outcomes of HCT has been emphasized in studies. Indolent non-Hodgkin lymphoma (NHL) patients who underwent allo-HCT with RIC has favorable outcomes (HR: 0.4, p=0.045) compared to the Hodgkin lymphoma and aggressive NHL patients.[111,112] In a systematic review/meta-analysis, for chronic lymphocytic leukemia (CLL), despite the lack of randomized studies for MAC and RIC, more commonly used regimens are RIC.[113] CLL working party of EBMT reported no difference in 5-year OS, EFS, and NRM outcomes of non-myeloablative (NMA), and RIC regimens (RIC: 46%, 38%, 35% and NMA: 52%, 43%, 32%, respectively).[114]

The incidence of allo-HCT has been decreased after the introduction of tyrosine kinase inhibitors in chronic myeloid leukemia (CML).[115] Despite the excellent outcomes of the tyrosine kinase inhibitors (TKI) in the CML, allo-HCT holds its place in the treatment of the multiple TKI resistant conditions. RIC regimens have been preferred due to the strong GVL effect in CML.[116,117] In a study based on the CIBMTR database, shows that there is no significant difference in adult CML patients who underwent allo-HCT with MAC and RIC in terms of OS, NRM, and LFS. But, RIC provides lower cGVHD rates (HR, 0.77; P 5 .02).[118]

Despite allo-HCT is also still the only curative therapeutic option for primary and secondary myelofibrosis, it is associated with noteworthy treatment-related morbidity andmortality.[119] Patients with intermediate-2 and high risk can be a candidate for allo-HCT. Fludarabine based RIC regimens have been widely used with promising event-free survival (EFS), and OS rates.[120]

In a study that compares Flu-Bu, Flu-Mel, FBM (Fludarabine, BCNU, Melphalan) based reduced-intensity regimens in myelofibrosis patients, there is no differences between treatment arms in terms of survival (47% , 46%, and 32%, p=0.55), grade2-4 acute GVHD (47%, 68%, and 68%, p=0.31), relapse mortality (29%, 14%, and 14% p=0.21), and NRM (29%, 41%, and 27%, p=0.32).[121] Kröger et al. analyze the transplantation outcomes of the primary and secondary myelofibrosis patients who underwent allo-HCT with busulfan (10 mg/kg)/fludarabine (180 mg/m2)– based RIC regimen. [122] In this prospective phase 2 trial, the mentioned RIC regimen has the outcomes of 51% 5-year EFS and 67%, OS. They also show that older than 55 years (HR: 2,7, p=0.02) and HLA mismatch (HR: 3.04; p= 0.006) are the risk factors for survival.

In severe aplastic anemia (SAA), allo-HCT from MSD is the first-line treatment choice in patients younger than 50-years old. The standard conditioning regimen for MSD transplantation is Cy (200mg/kg) and ATG.[123] In immunosuppressive therapy (IST) refractory patients older than 30-year old, fludarabine can be a less toxic alternative option for Cy.[124] Maury et. al demonstrate fludarabine-based conditioning regimen has shown survival benefit comparing to the cyclophosphamide-based conditioning (p=0.04).[125] The survival benefit might be related to lower graft failure rates (0% vs. 11%, p=0.09) in the fludarabine arm.

In thalassemia major, busulphan and cyclophosphamide-based conditioning regimen have been accepted as the gold standard for MSD allo-HCT for decades.[126] Disease-specific conditions such as secondary hemochromatosis secondary to multiple transfusions smooth the way to the hepatotoxicity of the By-Cy regimen. Mathew et al. demonstrate the treosulfan-based regimen

(treosulfan- thiotepa- fludarabine) reduces the incidence of sinusoidal obstruction syndrome (SOS) (78% to 30%; P = 0.000) and TRM (46% to 13%; p = 0.005) in high risk thalassemia major patients.[127]

In primary immunodeficiency diseases, conditioning regimens may not be needed if matched sibling bone marrow sources are preferred. [128,129] Drovac et al. demonstrated that URD transplantation can be performed without a conditioning regimen and show comparable OS (71% versus 92%, p<0.01), aGVHD (50% versus 39%, p<0.01), cGVHD (22% versus 5%, p<0.01), EFS outcomes with MSD HCT.[130] Inborn error working party (IEWP) recommends fludarabine-busulphan or fludarabine-treosulphan-based conditioning regimens.[131]

Despite its effectiveness, physicians search for alternatives of TBI because of secondary malignancies and organ damage such as pneumonitis, infertility, and veno-occlusive disease.[132] In this regard, targeted radiotherapy via radiolabeled monoclonal antibodies can spare the vital organs, and give the advantage of potentiating the effective radiotherapy dosing. Recently, ın a phase I study, Vo et al. report the efficacy of allo-HCT with Yttrium-90-labeled anti-CD45 antibody radio-conjugate based RIC in elderly patients with active leukemia or MDS.[133] Yttrium-90-labeled anti-CD45 antibody radio-conjugate combined conditioning regimen results in CR for the 87% of the patients. 1-year relapse rate, two-year OS are found as 41% and 46% respectively. Cabrero et al. conducted a phase II clinical trial to investigate the effects of Y-90 ibritumomab-tiuxetan as part of RIC allo-HCT in high-risk NHL patients.In this study, both of the two year OS and EFS is found 80%.[134]

**5) GVHD prophylaxis**

GVHD is one of the major complications of allo-HCT. Traditional GVHD prophylaxis with calcineurin inhibitors stayed insufficient especially with the introduction of new allo-HCT modalities.[135] Approximately thirteen years ago, Storb et. al. show cyclosporine (CSA) and methotrexate (MTX) have lower acute GVHD rates (33% versus 54%, p=0.014) comparing to the CSA alone prophylaxis.[136] Up to now, calcineurin based GVHD prophylaxis is widely accepted as a gold standard. Although there is no prospective randomized study, several researchers have attempted modalities of calcineurin-free GVHD prophylaxis.[137-139] A phase II prospective study conducted by Bejanyan et al., compares CSA and MMF combination with sirolimus and MMF combination.[139] Calcineurin-free prophylaxis did not differ in aGVHD rates, OS and PFS outcomes but lowered infection and TMA rates. Recently, a meta-analysis that compares CSA and tacrolimus combinations with MTX shows tacrolimus combination with MTX has lower grade 2-4 aGVHD (OR: 0.42 ; p<0.0001), cGVHD (OR: 0.79 ; p= 0.015) and NRM (OR: 0.62; p=0.03) and better OS (OR:1.3 ; p<0.0001) outcomes.[140] Mycophenolate mofetil (MMF) can also be combined with calcineurin inhibitors instead of MTX, especially in non-myeloablative conditioning regimens.[141] Abatacept, which is an inhibitory protein of T cell costimulation, tested in a phase I trial for GVHD prophylaxis in combination with tacrolimus and methotrexate. Combination of abatacept for GVHD prophylaxis was found safe and the rate of grade II-IV aGVHD was 28,6% at day 100. [142] Similarly, a retrospective study set out to determine whether abatacept combination with CSA and methylprednisolone is effective compared to standard

GVHD prophylaxis with tacrolimus and MMF in patients with beta-thalassemia. The study shows that none of the patients in abatacept combination group experienced grade III-IV aGVHD (0% vs 50%, p=0.001) or graft failure.[143] To investigate the role of CXCR5 blocking with maraviroc in GHVD prophylaxis, Reshef et al. carried out a phase II trial which demonstrate that grade III-IV acute GVHD at day 180, 1-year moderate to severe cGVHD were 5±4% and 8±5% respectively.[144] A meta-analysis indicates that mesenchymal stromal cells in GVHD prophylaxis setting improved OS rate and decreased the grade IV aGVHD.[145] In a prospective study, the combination of ruxolitinib and PT-Cy is used for GVHD prophylaxis in primary or secondary myelofibrosis patients. The rate of aGVHD grade II–IV and grade III-IV were 25% and 15% respectively. In total twenty of the patients, eleven patients (55%) experienced severe poor graft function and one patient primary graft failure.[146] Initially, Luznik et al. showed the bidirectional cytotoxic T-cell tolerance effect of PT-Cy. It is found efficient in preventing GVHD by selectively eliminating T cells and can result in durable engraftment.[147] Consideration of PT-Cy on ameliorating the detrimental effect of HLA disparity, it has been highly encouraged in the haploidentical allo-HCT setting. It has also been found as a rational option in MUD and MSD allo-HCT in recently published data.[148-151] One of the unanswered questions is whether PT-Cy or ATG will be superior over others. Battipaglia et al. compared ATG with PT-Cy in 9/10 matched allografted AML patients. The study showed that PT-Cy may show more favorable GRFS (37% versus 21%, p<0.03) outcomes without a survival advantage (56% versus 38%, p=0.07).[152] Invivo T cell depletion with ATG has been widely used in unrelated allo-HCT. Indications, type of ATG, and dosing have been discussed in different studies. It seems to be better to choose the

optimal dose for ATG depending on donor type, conditioning regimen preferences, absolute lymphocyte count just before ATG infusion, ethnicity, and GVHD prophylaxis preference.[153]

### 6) GVHD treatment

Cumulative incidences of grade 3-4 acute GVHD range between 39%-59% according to the stem cell source, donor type, and conditioning regimen.[154] Although the first-line treatment of GVHD is corticosteroids, second-line treatment remains challenging.

In a recently published randomized phase III trial, ruxolitinib has durable overall response rates in corticosteroid resistant aGVHD (40% versus 22% , $p<0.001$) with a tolerable the safety profile in comparison with patients who were treated with the best available therapy.[155] A phase 1 study of pacritinib, Jak-1 inhibitor, 75% of the treatment-naive aGVHD patients has at least partial response at day 28, in the steroid-refractory aGVHD patients the 28-day overall response rate (ORR) is found 70.6%.[156] Magenau et al. showed with a prospective phase II study that a1-antitrypsin (AAT), a serine protease inhibitor, may also find a role in steroid-resistant aGVHD treatment. The treatment responses were sustainable in around two-thirds of the patients without any need for additional immunosuppression.[157] A Phase 2/3, Multicenter, randomized study of AAT in patients aGVHD has been ongoing (MODULAATE Study, NCT03805789). In a phase 1b trial, vedolizumab as an anti-α4β7 integrin monoclonal antibody shows ORR in 79% (n=23) of the patients, 28% (n=8) of the patients has a CR.[158] Recently, in a phase III trial, human mesenchymal stromal cells have been induced more favorable ORR at day

100 in the steroid-refractory acute GVHD patients comparing with the prespecified control group. (70,4% versus 45%, respectively, p= .0003).[159]

Chronic GVHD is the major long term consequence for the allo-HCT survivors.[160] In 2017, the Food and Drug Association (FDA) approved ibrutinib as the first drug approval for cGVHD treatment in which patients failed with one or more-line treatment. Ibrutinib is a selective inhibitor of Bruton tyrosine kinase (BTK) proteins and also interleukin-2 inducible kinase (ITK) which has a role in T cell activation.[161] Miklos et al conducted a phase 1b/2 study for testing safety and efficacy of ibrutinib in patients with cGVHD who were non-responders to corticosteroid therapy and at least one-line therapy. The ORR was 67%, with a CR rate of 21% and a PR rate of 45%.[162]

Graft failure is a substantial handicap in allo-HCT. Growth factors for tri-lineage such as eltrombopag, recombinant human erythropoietin, and granulocyte stimulating agents can be used successfully in the treatment of graft failure.[163,164] A second allo-HCT can also be a solution. [165]

**7) Supportive care:**

Infections are the leading causes of mortality during allo-HCT especially, in the early post-transplantation period.[166] Not only the bacterial and fungal but also viral infection risk has been increased.[167] Cytomegalovirus (CMV) reactivation has been associated with poor allo-HCT

outcomes; can induce graft failure or non-relapse mortality.[158,168] CMV treatment may also result in myelosuppression as an adverse event.

Letermovir, an antiviral drug that inhibits the subunit of UL56 in the terminase complex that is essential for viral replication, has been approved for prophylaxis of CMV by FDA.[169] In the multicenter phase III trial prophylactic letermovir resulted in lower reactivation rate and all-cause mortality comparing to the placebo group without prominent myelosuppression.[170] Maribavir is another antiviral drug active against CMV infections even in ganciclovir, foscarnet, or cidofovir resistant strains.[171] Maertens et al. investigated maribavir efficacy on CMV reactivation comparing with valganciclovir in patients with transplantation (solid organ transplantation and allo-HCT) in a phase II randomized dose-ranging study in which response rates is found similar between two groups and also in maribavir dosing groups (400mg, 800mg, 1200mg PO, BID) Severe adverse event rates were higher in maribavir groups (44% vs 32%).[172] Prophylactic maribavir trial has been ongoing.

**In conclusion,** in recent years, there is promising advancement in the state of art for allo-HCT regarding GVHD prophylaxis and treatment, optimizing the conditioning regimen in the disease and individual basis, novel HLA typing methods, more available alternative donor sources, and supportive care. For the vast majority of the hematologic diseases, allo-HCT seems to remain the only curative therapeutic option.

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