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Modern strategies to reduce non-relapse mortality in allogeneic hematopoietic cell transplantation in the modern era: improving donor selection and patient selection

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MODERN STRATEGIES TO REDUCE NON-RELAPSE MORTALITY IN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN THE MODERN ERA: IMPROVING DONOR SELECTION AND PATIENT SELECTION

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IL MEDICO DEVE IMPARARE A PENSARE COME UN PAZIENTE

Doctor must learn to think as a patient

(Dr. Gianni Bonadonna)

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INDEX

ABBREVIATIONS

AL-EBMT = Acute Leukemia - European Society for Blood and Bone Marrow Transplant

AlloHCT = Allogeneic Hematopoietic Cell Transplant

ATG = Anti-thymocyte Globulin

AUC = Area Under the Curve

BM = Bone Marrow

CIBMTR = Center for International Bone Marrow Transplant Research

DRI = Disease Risk Index

EASIX = Endothealial Activation and Stress Index

EBMT = European Society for Blood and Bone Marrow Transplant

HLA = Human Leukocyte Antigen

GFRS = Graft-free Relapse-free Survival

GVHD = Graft-Versus-Host-Disease

GVL = Graft-versus Leukemia

HCT-CI = Hematopoietic Cell Transplant – Comorbidity Index

HL = Hodgkin Lymphoma

HR = Hazard Ratio

MAC = Myeloablative Conditioning

MRD = Matched Related Donor

MUD = Matched Unrelated Donor

NHL = Non-Hodgkin Lymphoma

NMDP = National Marrow Donor Program

NRM = Non-Relapse Mortality

OM = Overall Mortality

OS = Overall Survival

PAM = Pretransplant Assessment Mortality

PBSC = Peripheral Blood Stem Cells

PFS = Progression-free Survival

PTCy = Post-transplant Cyclophosphamide

RIC = Reduced-Intensity Conditioning

RI/POD = Relapse Incidence/Progression of Disease

TBI = Total Body Irradiation

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format.

The thesis consists in one objective and two articles:

1)**Authors**: **Alberto Mussetti**, Abraham S. Kanate, Tao Wang, Meilun He, Mehdi Hamadani, Herve Finel Sr., Ariane Boumendil Sr., Bertram Glass, Luca Castagna, Alida Dominietto, Joseph McGuirk, Didier Blaise, Zafer Gulbas, Jose Diez-Martin, Steven G.E. Marsh, Sophie Paczesny, Shahinaz M. Gadalla, Peter Dreger, Mei-Jie Zhang, Stephen R. Spellman, Stephanie J. Lee, Yung-Tsi Bolon, **Anna Sureda**.

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THESIS SUMMARY

Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is a lifesaving procedure for several oncological and non-oncological diseases. However, the higher mortality related to the toxicity of the transplant limits the curative potential of such a therapeutic strategy. The improvement of pre-transplant factors which could be modified from the physician have the potential to reduce the toxicity and increase the survival rates without complex specific interventions. A better selection of donors and patients represents a key aspect in decreasing transplant mortality.

Hypothesis

First study: we hypothesized that when using post-transplant cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis, the use of a matched-unrelated donor (MUD) or of a haploidentical one would have same clinical outcomes.

Second study: we hypothesized that a prognostic score made through the use of artificial-intelligence methods, would be superior to standard scores in terms of clinical outcomes predicticion.

Objectives

The aim of this project is to take advantage of international networks and registry-derived data to improve the evaluation of donor and patient selection.
1)in the first study, we will perform a comparison between the use of a MUD and a haploidentical donor in the setting of patients affected by lymphoproliferative diseases who have received an allogeneic hematopoietic cell transplantation when using PTCy as GVHD prophylaxis. The two cohorts will be compared in terms of the following outcomes: overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), relapse incidence/prograssion of disease (RI/POD), acute GVHD, chronic GVHD.

2)in the second study, we will create a newer personalized prognostic score which will be built through the use of registry-derived big data and will allow to calculate survival outcomes for alloHCT. Six artificial-intelligence derived scores will be compared to standard logisitic regression analysis in terms of overall mortality (OM) and NRM prediction capacity. The results will be compared, and the best method will be used to generate survival prediction across the study population.

Methods

First study: we will perform a retrospective study with clinical data deriving from two international transplant registries (European Society for Blood and Marrow Transplantation Society EBMT, Center for International Bone Marrow Transplant Research CIBMTR). We will work together with the statistical team of the registries to perform a data cleaning of the database. Thereafter, a retrospective analysis (univariate/multivariate) will be performed and adjusted depending on the dataset characteristics.

Second study: we will rely on big data derived from 33.927 patients who received alloHCT for hematological diseases registered into the EBMT registry from 2010 to 2019. The primary endpoint of the study will be to build a personalized prediction model able to calculate the OM and the NRM of alloHCT. Both classical multivariate logistic regression model and newer machine learning methods will be used.

Results

First study: A total of 2140 adults (34% CIBMTR, 66% EBMT) aged >18 years who received their first haploidentical alloHCT or MUD (8/8 match at HLA-loci A, B, C, and DRB1) for lymphoma using PTCy-based GVHD prophylaxis from 2010 to 2019 were retrospectively analyzed. The majority of both MUD and haploidentical alloHCT received reduced intensity/nonmyeloablative (RIC/NMA) conditioning (74% and 77%, respectively) and used a peripheral blood stem cell (PBSC) graft (91% and 60%, respectively) and a 3-drug GVHD prophylaxis (PTCy + calcineurin inhibitor + mycofenolate mofetil in 54% and 90%, respectively). Haploidentical alloHCT has less favorable results versus MUD cohort in terms of OM (hazard ratio [HR= = 1.69; 95% confidence interval [CI], 1.30-2.27; P < .001), PFSl (HR=1.39; 95% CI, 1.10- 1.79; P = .008), NRM (HR = 1.93; 95% CI, 1.21-3.07; P = .006), platelet engraftment (HR = 0.69; 95% CI, 0.59-0.80; P < .001), acute grade 2-4 GVHD incidence (HR =

1.65; 95% CI, 1.28-2.14; P < .001), and chronic GVHD (HR = 1.79; 95% CI, 1.30-2.48, P < .001). No significant differences were observed in terms of RI/POD and neutrophil engraftment. Adjusting for propensity score yielded similar results.

Second study: The analysis included 33,927 patients. The model for OM was trained, optimized, and validated using 70%, 15%, and 15% of the data set, respectively. The top models, “gradient boosting” for OM (area under the curve = 0.64) and “elasticnet” for NRM mortality (area under the curve = 0.62), were selected. In the final prognostic model, patients with the lowest score had a 2-year OM and NRM of 18 and 13%, respectively, while those with the highest score had a 2-year OM and NRM of 82 and 93%, respectively. The results were consistent in the subset of the haploidentical cohort (n = 4386).

Conclusions

In relation to improving donor characteristics, whenever a matched-related donor is not available, a MUD should be preferred over a haploidentical donor (if available in a timely manner) when using PTCy-based GVHD prophylaxis for patients with lymphomas.

Regarding patient selection, newer prognostic scores made with artificial intelligence allow a personalized risk stratification in terms of OM and NRM. However, do not significantly improve mortality prediction when compared to standard prognostic scores. This study evidences the need for more precise and personalized markers to improve survival prediction.

Introducció

El trasplantament al·logènic de progenitors hematopoètics és un procediment curatiu per a diverses malalties oncològiques i no oncològiques. Tanmateix, la gran/no despreciable mortalitat relacionada amb la toxicitat del trasplantament limita el potencial curatiu d'aquesta estratègia terapèutica. L'optimització prèvia al trasplantament dels factors modificables té el potencial de reduir la toxicitat i augmentar les taxes de supervivència sense intervencions específiques complexes. Una millor selecció dels donants i pacients representa un aspecte clau per a disminuir la mortalitat del trasplantament.

Hipòtesi

Primer estudi: Vam suposar que, en la utilització de ciclofosfamida post-trasplantament per a la profilaxi de la malaltia empelt contra hoste, l'ús d'un donant no emparentat compatible o d'un donant haploidèntic tindria els mateixos resultats clínics.

Segon estudi: Vam formular la hipòtesi que un índex pronòstic creat mitjançant mètodes d'intel·ligència artificial seria superior als índex pronòstics estàndard en termes de predicció de resultats clínics.

Objectius

Aquest estudi té com a objectiu aprofitar les xarxes internacionals i les dades obtingudes de registres per a millorar l'avaluació de la selecció dels donants i pacients en el context del trasplantament al·lògènic de progenitors hematopoètics. 1) En aquest primer estudi compara l'ús d'un donant no emparentat compatible i un donant haploidèntic en pacients afectes de sindromes linfoproliferatives que han rebut un transplantament basat en la ciclofosfamida post-trasplantament com a profilaxi de la malaltia empelt contra hoste. Compararem les dues cohorts pel que fa als següents resultats: supervivència global, supervivència lliure de progressió, mortalitat no relacionada amb la recaiguda, incidència de recaiguda/progressió de la malaltia, malaltia empelt contra hoste aguda i malaltia empelt contra hoste crònica.

2) En el segon estudi, crearem un nou índex pronòstic personalitzat mitjançant l'aplicació de mètodes d'intel·ligència artificial sobre dades massives obtingudes de registres. Aquest sistema permetrà calcular la mortalitat no relacionada amb la recaiguda derivada del transplantament. Sis sistemes de puntuació basats en intel·ligència artificial es compararan amb l'anàlisi de regressió logística estàndard en termes de capacitat de predicció de la mortalitat global i la mortalitat no relacionada amb la recaiguda. Es compararan els resultats i s'utilitzarà el millor mètode per generar prediccions de supervivència per a tota la població de l'estudi.

Mètodes

Primer estudi: realitzarem un estudi retrospectiu amb dades clíniques derivades de dos registres internacionals de trasplantament (Societat Europea de Trasplantament de Sang i Medul·la Òssia, Centre de Recerca de Trasplantament de Medul·la Òssia Internacional). Treballarem conjuntament amb l'equip de bioestadística dels registres per a dur a terme una neteja de dades de la base de dades. Posteriorment, es realitzarà una anàlisi retrospectiva (univariada/multivariada) i s'ajustarà en funció de les característiques del conjunt de dades.

Segon estudi: ens basarem en dades massives o “big data” derivades de 33.927 pacients que van rebre un trasplantament al·logènic de progenitors hematopoètics per malalties oncològiques registrades al registre de la Societat Europea de Trasplantament de Sang i Medul·la Òssia, des de 2010 fins a 2019. El principal objectiu de l'estudi serà construir un model de predicció personalitzat capaç de calcular la mortalitat global i la mortalitat relacionada amb la toxicitat del trasplantament al·logènic de progenitors hematopoètics. Es farà servir tant un model de regressió logística multivariant clàssic com mètodes d'aprenentatge automàtic més recents.

Resultats

Primer estudi: En total, es van analitzar de manera retrospectiva 2.140 adults (34% del Centre de Recerca de Trasplantament Internacional de Sang i Medul·la Òssia, 66% del Societat Europea de Trasplantament de Sang i Medul·la Òssia) majors de 18 anys que van rebre el seu

primer trasplantament al·logènic de progenitors hematopoètics de donant haploidèntic o de donant no emparentat compatible (coincidència 8/8 en els loci HLA A, B, C i DRB1) per limfoma utilitzant profilaxi de la malaltia empelt contra hoste amb ciclofosfamida post-trasplantament de 2010 a 2019. La majoria dels donants no emparentats compatibles com donants haploidèntics van rebre un condicionament d'intensitat reduïda/no mieloablativa (74% i 77%, respectivament) i van fer servir com a font progenitors hematopoètics provinents de sang perifèrica (91% i 60%, respectivament) i profilaxi contra la malaltia d'empelt contra l'hoste basada en de tres fàrmacs(ciclofosfamida post-trasplantament + inhibidor de la calcineurina + micofenolat mofetil en 54% i 90%, respectivament). El trasplantament al·logènic haploidentic té resultats menys favorables en comparació amb la cohort de donants no emparentats compatibles en termes de mortalitat global (hazard ratio [HR] = 1,69; interval de confiança del 95% [IC], 1,30-2,27; P <0,001), supervivència lliure de progressió (HR = 1,39; IC del 95%, 1,10-1,79; P = 0,008), mortalitat no relacionada amb la recaiguda (HR = 1,93; IC del 95%, 1,21-3,07; P = 0,006), injert plaquetar (HR = 0,69; IC del 95%, 0,59-0,80; P <0,001), incidència de la malaltia empelt contra hoste aguda grau 2-4 (HR = 1,65; IC del 95%, 1,28-2,14; P <0,001) i malaltia empelt contra hoste crònica (HR = 1,79; IC del 95%, 1,30-2,48; P <0,001). No es van observar diferències significatives en termes de recidiva/progressió de la malaltia i injert de neutròfils L'ajust pel punt de propensió va produir resultats similars.

Segon estudi: L'anàlisi va incloure 33.927 pacients. El model per a la mortalitat global va ser entrenat, optimitzat i validat utilitzant el 70%, el 15% i el 15% del conjunt de dades, respectivament. Els models principals, "Gradient boost" per a la mortalitat global (àrea sota la corba = 0,64) i "elasticnet" per a la mortalitat no relacionada amb la recaiguda (àrea sota la corba = 0,62), van ser seleccionats. En el model pronòstic final, els pacients amb la puntuació més baixa tenien una mortalitat global i una mortalitat no relacionada amb la recaiguda als dos anys del 18% i del 13%, respectivament, mentre que aquells amb la puntuació més alta tenien una mortalitat global i una mortalitat no relacionada amb la recaiguda als dos anys del 82% i del 93%, respectivament. Els resultats van ser consistents en el subconjunt de la cohort de trasplantament haploidèntic (n = 4,386).

Conclusions

En relació amb la millora de les característiques del donant, sempre que no hi hagi disponible un donant relacionat compatible, es preferible elegir a un donant no emparentat compatible sobre un donant haploidentic (si està disponible de manera oportuna) quan s'utilitza profilaxi contra la malaltia empelt contra hoste basada en ciclofosfamida post-trasplantament per a pacients amb limfomes.

Pel que fa a la selecció del pacient, els nous índex pronòstics creats amb metodologia d'intel·ligència artificial permeten una estratificació del risc personalitzada en termes de mortalitat global i mortalitat no relacionada amb la recaiguda. No obstant això, aquests índex no semblen millorar significativament la predicció de la mortalitat en comparació amb els índex pronòstics estàndard. Aquest estudi evidencia la necessitat d'índex més precisos i personalitzats per millorar la predicció de la supervivència.

INTRODUCTION

Allogeneic hematopoietic cell transplant and toxicity from a historical perspective

AlloHCT is a lifesaving procedure for several malignant and non-malignant diseases. Over the last 50 years, over 1 million of alloHCT have been performed worldwide. (1) Despite being in many cases the only therapy with the potential to cure blood diseases, it is also considered the most complex therapeutic strategy with the highest short-term and long-term toxicity in the field of Hematology. AlloHCT represents the convergence of different scientific discoveries and each one of these is responsible for toxicity. The use of chemotherapy and radiotherapy, the compatibility between the donor and the recipient, and the risk of infectious diseases after the transplant are just a few of the main barriers which have been encountered by transplant physicians since the first application of such strategy. To clarify such a complex scenario, a historical perspective is useful to understand how each of these factors was discovered and solved or improved.

The beginning of research related to bone marrow (BM) transplantation dates back to the Second World War. In fact, with the use of nuclear weapons, it was observed that those people who were not killed in the blast, started developing specific and common toxicities such as cutaneous lesions, nausea, diarrhea, bleeding gums, fever, and hair loss. Such syndrome, known as “the atomic bomb disease”, was related to the damage of radiation in the marrow leading to aplasia. (2) Such complications generally lead to death due to infections. During the following years, with the fear of the Cold War and the risk of a nuclear apocalypse, the US government started funding medical research related to therapeutic approaches to cure severe marrow aplasia following exposition to radiation. The start of BM transplantation research is usually referred as the first experiments of Jacobson at the University of Chicago leading to the observation that hematopoiesis was preserved in mice after lethal irradiation if the spleen was shielded. (3) A few years later, it was Lorenz from the National Cancer Institute who started investigating whether cells from the shielded spleen were reseeding the hematopoietic system after radiation. To test this, he showed that mice

recovered from radiation injury when infused with BM after a lethal dose of radiation. (4) The final proof of the cellular theory was performed by Charles Ford, working at the Radiation Research Unit in Harwell, Berkshire. He figured out how to visualize chromosomes in mammalian cells and he studies the effect of radiation on chromosomes. In 1955 he identified a strain of mice with radiation-induced structural change, the "T6" abnormality. Then, he irradiated mice that lacked this chromosomal marker and infused them with BM cells of mice with the T6 abnormality. When the irradiated mice recovered, their blood cells presented the abnormality finally proving the cellular theory of radiation protection. (5)

Once it was recognized how to repopulate BM, attention focused on the therapeutic effect of radiation against leukemia. The idea of using lethal doses of radiation to clear leukemic cells from marrow and then transplant a mouse came from Barnes and colleagues. In 1956, they treated mice with lethal doses of radiation and then transplanted them with a cure for their leukemia. (6) In 1957 Thomas and colleagues started infusing allogeneic BM into human patients. With the first six patients, the aim was to test if the BM (collected from death adults or fetus) was not toxic to be infused into another human body. Only in one of these first six patients it was observed a transient presence of allogeneic red cells after the infusion, However, in all cases a non-engraftment or rejection was reported. (7) Following these first observations, it was clear how basic science discoveries were needed to better understand the immunology of transplants. HLA-barrier was not known at that time. Thomas and colleagues, in order to avoid an immunological rejection, started to perform transplants only in patients with a homozygous twin. The first two patients were children with leukemia. In the first case, the use of 1100 rads of total body irradiation and then transplant marrow from her identical twin. (8) After the initial recovery, leukemia reappeared, and the patient died of disease. To test higher doses of total body irradiation, from 1400 to 2000 rads, other leukemia patients were treated using identical twin family members. All patients died of disease relapse, infection or in 1 case of liver insufficiency. (9) In 1960, Nancy Lowry, a six-year child with aplastic anemia (a non-oncological disease) and an identical twin, were sent to Thomas to perform a marrow transplant. In this case, considering the no risk of disease relapse and the absence of graft rejection, a transplant was tried. Finally, Nancy recovered without severe complications nor disease relapse. (10) In the 1960s, other experiments were made without

significant success showing how significant scientific immunological discoveries were needed for a safer and more effective marrow transplant. (11)

Research in animal models continued and several key observations were made. Billingham and colleagues described for the first time in transplanted mice a syndrome characterized by diarrhea, skin rash which they called runt disease, now known as graft versus host disease (GVHD). Uphoff showed that this reaction was mediated by genetic factors.(12) Snell finally described the presence of histocompatibility antigens influencing graft tolerance in mice. (13) Storb proved that cyclophosphamide could be used instead of total boy irradiation for conditioning prior to transplant. (14) Epstein described the existence of dog leukocyte antigen system, fundamental for the risk of graft failure and GVHD. (15) Methotrexate was able to prevent or reduce the risk of graft versus host disease in canine models. (16)

Due to a general improvement in basic science knowledge and chemotherapeutic agents, Thomas restarted with transplant to treat leukemia using identical HLA-matched sibling or twins. During the initial part of the 1970s, the Seattle group performed almost a hundred transplants. (17,18) Among the thirty-seven patients with aplastic anemia, almost half were alive with normal graft. Of the seventy patients with acute leukemia, ten were alive and in remission after one to four years after transplant. As Thomas wrote in the paper, it was becoming clear that a cure for hope for otherwise untreatable diseases was possible. In this fundamental paper, three major obstacles to transplant were described: GVHD, infections and disease recurrence.

Little was known about GVHD at that time. Methotrexate was used to prevent it, but its treatment was difficult. It is curious how in the 1975 paper, nineteen patients with acute GVHD were treated with anti-thymocyte globulin produced from the Seattle center. From the 1970s to the 1980s, several transplant investigators focused on reducing GVHD incidence and treatment. When the role of T cells in GVHD development was established, the use of T cell inhibitory drugs was integrated into alloHCT platforms. Methotrexate was already been used

and other drugs such as cyclosporine were added to this backbone. (19) Also, during the same time, T-cell depletion strategies started to be used in the clinical practice. (20) Finally, a better understanding of acute, but not chronic, GVHD was made elucidating the three main mechanisms related to this human-made disease: 1) tissue damage and inflammation due to the conditioning regimen; 2) priming of donor T-cells; 3) effector phase mediated by cellular and humoral factors leading to tissue destruction. (21) The development of GVHD also made possible for the first time the recognition of a graft-versus-leukemia (GVL) effect. It was in 1979 when for the first time it was reported that patients who developed GVHD had a 2.5 lower risk of developing leukemia recurrence after transplant. Other studies showed directly or indirectly the existence of such phenomenon through the demonstration of increased relapse rate when using *ex-vivo* T-cell depletion, (22) disease remission induction through the removal of immunosuppressant drugs, (23) the efficacy of donor leukocyte infusion to treat disease recurrence after transplant, (24) a higher relapse incidence in recipients of syngeneic grafts. (25) Thanks to these discoveries, it became clear that tumors could also be attacked by the immune system and not only by chemo or radiotherapy. Infections were the second big problem after transplant identified by the Thomas group. It was already known that a low neutrophil count was associated with increased bacterial infection. For this reason, the Seattle group performed transplants using prophylactic antibiotics (streptomycin and penicillin at that time) and granulocyte infusions and placing the patients in laminar air flow rooms. With such approaches, only a few patients died of infection within the first month after transplant in the 1975 paper. However, it was clear that even after the engraftment of neutrophils, other non-bacterial infections could arise. The most alarming were those related to a rapid progressive lung disease termed interstitial pneumonia occurring in one third of patients. The autopsy of such cases revealed cytomegalovirus or *Pneumocystis carinii* infection.

At that time, no therapies were available for both infections. Finally, the third issue was related to disease recurrence. In fact, the majority of patients who did not die of complications died of leukemia relapse. In the fundamental 1975 paper, two other important problems were not described: the unavailability of donors in case of HLA-

related donor absence and the limitation of transplant procedure only to young and fit patients.

Expanding donor pool

By the late 1970s, it was known that the HLA system was quite complex and heterogeneous. Initially, only HLA-A, HLA-B and HLA-DR were known, and dozens of varieties were identified at that time. For that reason, only syngeneic or HLA-matched siblings were used at that time. At the beginning of the 1980s, a few organizations such as the ones started by Anthony Nolan's mother (Anthony Nolan registry) or Laura Graves' father (the NMDP registry) started collecting HLA data from unrelated donors. Laura Graves was ten-years old when she received a transplant from an HLA-matched unrelated donor compatible at A, B and DR loci for acute lymphocytic leukemia. The donor was a technician of the Hansen's lab at the Fred Hutchinson Hospital where Laura was brought to receive her transplant. Laura was discharged after three months without disease or GVHD. (26) This case and other examples gave rise to the creation of different donor registries worldwide which, under the umbrella of the World Marrow Donor Association allows to find a suitable unrelated donor whenever necessary. (27) Another way to overcome HLA barriers was represented by the use of cord blood or familial haploidentical donors. Cord blood graft requires less stringent HLA compatibility and an inferior risk of GVHD. This is in part mediated by a higher content of naive donor-derived T-cells. (28) However, a decreased number of progenitor stem cells in the unit are responsible for a slower immune reconstitution with an increased risk of infections (especially viral infections) and a higher non-relapse-mortality (NRM). The use of double cord unit has not improved such issue. (29) The addition of nicotinamide has proved to be useful in reducing engrafting time and thus infectious complications. (30) However, the higher cost of such type of transplant in association with a higher toxicity-related-mortality brought to a decline in such technique worldwide. (31) The second approach to overcome the HLA barrier is to use a haploidentical donor. This technique has the advantage of using an almost universal donor (parents or sons or siblings) without the need for necessary administrative time delays related to the use of a registry donor. One of the first way to perform such transplant was to use an elevated number of CD34+ cells ("megadose") and *ex-vivo* removal of T cells from donor graft to reduce GVHD incidence.(32) Despite being innovative, such type of transplant was

characterized by a very high NRM due to infections and also a considerable disease progression or relapse. A safer approach was developed by researchers at John Hopkins Cancer center. This technique, based on the use of PTCy, was pioneered by George Santos, a friend and a competitor of Donnell Thomas. Santos worked at John Hopkins where he focused on the use of alkylating agents (busulfan and cyclophosphamide) as part of the conditioning instead of total body irradiation (TBI) which was not available at John Hopkins. He found that low-dose PTCy was as effective as methotrexate for GVHD prevention. Higher doses were not used since Santos was afraid of killing donor stem cells. Then, it was observed that a few patients treated with myeloablative doses of cyclophosphamide as part of the conditioning regimen recovered their own blood counts without donor-cell engraftment. In fact, it was later understood that stem cells can neutralize the cytotoxic effect of cyclophosphamide due to a high concentration of aldehyde dehydrogenase into their cytoplasm. Those observations led Santos and colleagues to study high dose cyclophophamide in murine models. In 1999, Dr. Richard Jones and Ephraim Fuchs at John Hopkins started using such a strategy in the clinical setting, starting with haploidentical donors. (33) This technique proved to be effective and rapidly changed the scenario for haploidentical donors.

Expanding patients' age

A fundamental part of the alloHCT process is the conditioning regimen. The functions of the conditioning regimen are three: 1) create new space for the donor' stem cells; 2) suppress of the recipient's immune system; 3) reduce disease (in the oncological setting). Initially, only myeloablative doses of radiotherapy were administered in order to obtain such results. (34) However, not all the hospitals could rely on TBI. For such reason, alkylating agents were started to be tested in this setting. One of the first examples of this was the substitution of TBI with busulfan and cyclophosphamide by Santos and colleagues at John Hopkins. (35) However, despite being effective, such conditioning regimens were characterized by a higher acute and long-term toxicity. Thus, alloHCT was considered only for young and fit patients which are a minority of hematological patients. At the end of the 1990s, a few groups started investigating the use of RIC/NMA conditioning regimens. In fact, at that time, there was enough evidence that the GVL effect was another mechanism of action of alloHCT against tumors. So, it was considered reasonable to reduce the intensity of the conditioning to reduce

acute toxicity and allow the new immune system to attack the tumor. Of course, if we lower the intensity of a conditioning regimen, it is possible that the chances of a graft rejection are higher because the recipient's immune system could persist. A solution to this problem was the introduction of drugs with a very powerful anti-lymphocyte effect such as fludarabine. In a personal communication, Dr. Sergio Giralt said that the idea of using fludarabine was related to a single episode. During the 1990s, acute myeloid leukemia experts at MD Anderson Cancer Center created and used a fludarabine-based reinduction chemotherapy called FLAGIDA to treat acute myeloid leukemia relapse. Patients with neutropenic fever were treated with antibiotics and allogeneic granulocyte infusions. One of the patients of Giralt, after infusions of granulocytes, started developing a syndrome which resembled acute GVHD, but the patients never received an alloHCT. Since fludarabine was known to be a powerful anti-lymphocyte agent, it was hypothesized that such an agent was responsible for the patient's severe lymphocyte immune suppression. Thus, the infusion of allogeneic granulocyte could have generated an acute GVHD. Since then, a series of trials showed how it is possible to reduce the conditioning intensity with lower toxicity. (36,37) Such benefit is counterbalanced by a higher relapse incidence. Currently, the use of improved version of older agents such as treosulfan or newer agents with less toxicity such as thiotepa brought to the creation of the so-called "reduced-toxicity regimen" which ideally should maintain the anti-tumor effect of a myeloablative conditioning regimen (MAC) while reducing the toxicity such as a RIC/NMA. (38) In the future, it is possible that the use of targeted agents such as anti-CD45 immunoconjugates also for the conditioning regimens could improve such results paving a new era for alloHCT. (39)

Donor-related risk factors: HLA compatibility in the post-transplant cyclophosphamide era

While advances in HLA matching and GVHD prevention have significantly improved alloHCT outcomes, the absence of a perfectly matched donor requires alternative strategies, such as haploidentical transplants or cord blood units. Early attempts at haploidentical transplants involved complex immunosuppressive strategies like T-cell depletion. (40) However, the downsides of these approaches, including increased risk of infections and immunological complications, often outweighed the benefits of alloHCT. A turning point came in the early

2000s with the introduction of high-dose PTCy for haploidentical alloHCT. (33) This simpler and more effective strategy achieves its success through potent immune tolerance induction, acting on both peripheral and central immune mechanisms. Building on successful proof-of-concept studies cited earlier, retrospective analyses suggest that haploidentical alloHCT with PTCy may rival standard calcineurin-inhibitor and methotrexate-based GVHD prophylaxis for MUD alloHCT. (41,42)

For HLA-identical donors, combining cyclosporine with methotrexate has been the gold standard GVHD prophylaxis for decades, with research by Storb et al. in the 1980s solidifying this approach through a randomized trial. (43) The success of methotrexate combined with cyclosporine for HLA-identical donors was replicated with tacrolimus in MUD transplants. Notably, both calcineurin inhibitors yielded similar results in GVHD prophylaxis. (44,45) Recent decades have seen the rise of *in vivo* T cell depletion with polyclonal anti-thymocyte globulin (ATG) for MUD alloHCT. This approach, evaluated in four successful randomized trials (one using rabbit ATG and three using anti-thymocyte lymphocyte globulin), has proven superior to standard calcineurin inhibitor and methotrexate regimens in reducing both acute and chronic GVHD. (46–49)

More recently, the search for the optimal partner to calcineurin inhibitors in GVHD prophylaxis for both related and unrelated donors shifted to PTCy, potentially replacing methotrexate, with or without ATG.

Haploidentical setting with PTCy

Pioneering work explored PTCy's role in haploidentical alloHCT within a NMA/RIC conditioning regimen (Hopkins' protocol). Subsequent trials established the optimal PTCy dose at 50 mg/kg on days +3 and +4, followed by a combination of mycophenolate mofetil and calcineurin inhibitors from day +5.(33) Real-world data from various retrospective studies involving different blood cancers suggest PTCy in haploidentical alloHCT achieves similar overall outcomes to those with standard donors with methotrexate-based GVHD prophylaxis (**Table**

1). Interestingly, PTCy appeared to be associated with a lower chronic GVHD rate compared to traditional calcineurin inhibitors-based prophylaxis for matched-related donor (MRD) or MUD. However, this might be due to the earlier predominance of BM use in the first haploidentical alloHCT studies. A landmark study by Ciurea et al. directly compared outcomes of PTCy-based haploidentical alloHCT to MUD transplants with standard calcineurin inhibitors prophylaxis. (41) While OS was similar, chronic GVHD was significantly lower with haploidentical alloHCT. This finding aligns with results from Kanate et al. who observed reduced chronic GVHD in lymphoma patients receiving PTCy-based haploidentical alloHCT with a RIC/NMA. (41) Over time, conditioning for haploidentical alloHCT has shifted from non-myeloablative to myeloablative approaches. The traditional Baltimore protocol, using fludarabine-cyclophosphamide with low-dose total body irradiation (200cGy), achieved low NRM but RI/POD rates. This led to a focus on more intensive conditioning regimens also in the PTCy setting. Growing experience in the past decade suggests that MAC conditioning can be well-tolerated with acceptable NRM in younger patients and those with high-risk diseases. Current conditioning regimens for haploidentical alloHCT often rely on alkylating agents like thiotepa, busulfan (6.4-9.6 mg/kg), melphalan (140 mg/m2), combined with fludarabine (150 mg/m2). Tailoring these regimens to each patient's underlying disease risk is crucial to balance the risks of RI/POD and NRM.

Study	**Disease**	**Number of patients**	**Type of conditioning**	**Grade 2-4 acute GVHD**	**All grade chronic GVHD**	**Relapse/NRM**	**OS**
Castagna(50)	HL	62	Flu/Cy/TBI, Thio/Flu/Cy/TBI	23%	16%	21%/20% at 1 year	63% at 1 year
Gauthier(51)	HL	34	Flu/Cy/TBI	28%	15%	28%/12% at 3 years	78% at 3 years
Martinez(52)	HL	98	RIC (90%)	33%	26%	39% at 2 years/17% at 1 year	67% at 3 years
Ciurea(53)	AML MDS	43	Flu/Mel based	35%	9%	24%/34% at 2 years	42% at 2 years

Gayoso(54)	AML MDS	64	Bu/Flu/Cy (MAC)	29%	28%	25%/19% at 2 years	56% at 2 years
Shem-Tov(55)	ALL	136	RIC, MAC	28%	44%	28%/23% at 3 years	54% at 3 years
Santoro(56)	ALL	208	RIC, MAC	31%	29%	37%/32% at 3 years	33% at 3 years
Prata(57)	AA	33	RIC	23%	20%	------	78% at 2 years
Comparison studies of haploidentical donor alloHCT versus 8 of 8 HLA-matched unrelated donor with standard GVHD prophylaxis							
Ciurea(41)	AML	Haplo=192 MUD=1982	Haplo = MAC 104; RIC 88 MUD = MAC 1245; RIC 737	MAC setting: 16% vs. 33% (p < 0.0001) RIC setting: 19% versus 28% (p = 0.05)	MAC setting: 30% vs. 53% (p < 0.0001) RIC setting: 34% versus 52% (p = 0.002)	No differences between haplo and MUD	MAC setting: 45% vs. 50% (p = 0.38) RIC setting: 46% versus 44% (p = 0.71)
Kanate(41)	NHL HL	Haplo = 185 MUD without ATG = 241 MUD with ATG = 491	RIC for all patients	Grade III-IV acute GVHD 8%, 12%, 17%	13%, 51% and 44% (p < 0.001)	No differences between haplo and MUD	60%,62%,50% (p = 0.02)

Table 1. Selection of studies using PTCy in the setting of haploidentical alloHCT. GVHD=Graft-versus-host-disease; NRM=non-relapse-mortality; OS=overall survival; HL=Hodgkin lymphoma; Flu=fludarabine; Cy=cyclophosphamide; TBI=total body irradiation; RIC=reduced-intensity conditioning; AML=acute myeloid leukemia; MDS=myelodysplasia; Mel=melphalan; Bu=busulfan; MAC=myeloablative; ALL=acute lymphoblastic leukemia; AA=aplastic anemia.

Adapted from Mussetti, A.; Paviglianiti, A.; Parody, R.; Sureda, A. Is Post-Transplant Cyclophosphamide the New Methotrexate (58)

Graft type for haploidentical alloHCT with PTCy

Pioneering trials of T-cell replete haploidentical alloHCT with PTCy primarily used bone marrow (BM) as the stem cell source. However, PBSC have become the standard for adult alloHCT worldwide due to their advantages over BM. These advantages include easier

collection, faster blood cell recovery, and a reduced risk of both graft failure and relapse. (59,60) The high T cell content of PBSCs initially raised concerns about an increased risk of GVHD in T-cell replete haploidentical alloHCT. Consequently, BM with its lower T cell count, became the preferred stem cell source for this approach. Despite concerns, subsequent studies demonstrated safe use of PBSCs in T-cell replete haploidentical alloHCT. These studies reported acceptable rates of acute and chronic GVHD, comparable to those seen with PBSC transplants from MRD or MUD. (61–63) However, some controversy persists, with large international registry data showing mixed results. A study compared outcomes in 681 patients receiving T-cell replete haploidentical alloHCT with either PBSCs or BM. While both groups showed similar rates of engraftment, NRM, and 2-year OS, the PBSC group experienced a higher incidence of acute and chronic GVHD but a lower risk of RI/POD.(64) Also, in a separate study in Hodgkin lymphoma (HL) patients showed better outcomes for PBSC, including GVHD-free, relapse-free survival (GRFS), OS, and PFS. (65)Adding to the debate, a large European retrospective study on 451 patients with acute leukemia (myeloid or lymphoblastic) undergoing haploidentical alloHCT found no significant differences in chronic GVHD, RI/POD, NRM, or leukemia-free survival between BM and PBSC recipients.(66) However, the PBSC group had a lower engraftment rate and a higher incidence of moderate-to-severe (grade 2-4) acute GVHD, suggesting a potential trade-off between relapse risk and GVHD. A recent analysis by the CIBMTR examined outcomes of PTCy haploidentical alloHCT in adults with various blood cancers. (67) They divided patients into four groups based on conditioning intensity (MAC vs. RIC/NMA) and stem cell source (BM vs. PBSC). While initial analysis suggested higher rates of moderate-to-severe acute and chronic GVHD with PBSC in both conditioning regimens, this was not confirmed in the multivariable analysis for acute GVHD. However, PBSC use emerged as a significant risk factor for chronic GVHD only in the RIC/NMA setting. Importantly, no differences in RI/POD or OS were observed between the groups. In conclusion, despite limitations inherent to retrospective studies, both BM and PBSC appear to be viable options for PTCy based haploidentical alloHCT. However, PBSCs may be associated with an increased risk of GVHD, particularly cGVHD in certain contexts. Future research should focus on identifying the optimal approach based on underlying disease characteristics and conditioning intensity.

HLA-identical and mismatched-unrelated donor setting with PTCy

Luznik et al. pioneered the use of PTCy alone for high-risk blood cancer patients receiving BM transplants from MRD or MUD in a MAC setting. (68) This approach achieved acceptable rates of acute GVHD (grade 2-4 GVHD: 43%, grade 3-4: 10% at day 100) and chronic GVHD (2-year all-grade GVHD: 10%). Additionally, the study reported favorable outcomes for 2-year NRM (17%), event-free survival (39%), and OS (59%). Similar results were reported by Kanakry et al., who employed busulfan/fludarabine instead of busulfan/cyclophosphamide for MAC conditioning. (69) Their study observed rates of acute GVHD at day 100 of 51% (grade 2-4) and 15% (grade 3-4). Non-relapse mortality, disease-free survival, and OS at one year were 16%, 62%, and 67%, respectively. In a separate analysis of a larger cohort (209 patients) receiving BM grafts with MAC, the same author reported a 45% rate of grade 2-4 acute GVHD at day 100. Three-year outcomes for this broader group showed a NRM of 17%, disease-free survival of 46%, and OS of 58%. (70) However, concerns regarding higher rates of severe acute GVHD have emerged with PTCy in the MAC-PBSC setting. Mielcarek et al. reported a high incidence of grade 2-4 acute GVHD (77% at day 100) using PTCy and cyclosporine with two different MAC conditioning regimens (busulfan/fludarabine and TBI) for high-risk malignancies. (71) To address the high acute GVHD rates observed with PTCy and PBSC in the MAC setting, some researchers opted to maintain the standard three-drug GVHD prophylaxis (PTCy, mycophenolate mofetil, and calcineurin inhibitor) even for HLA-matched donors. Carnevale-Schianca et al. reported promising results with this approach in 35 high-risk patients, achieving low rates of acute GVHD (12% all-grade GVHD) and favorable outcomes for NRM (3%), event-free survival (54%), and OS (77%) at two years.(72) Similarly, Greco et al. observed a moderate rate of grade 2-4 acute GVHD (23% at day 100) using PTCy with sirolimus (with or without mycophenolate mofetil). (73) However, their study also showed a higher RI/POD rate (36%) at one year compared to Carnevale-Schianca et al. A separate phase II study exploring PTCy with sirolimus alone reported even higher rates of both acute (46%) and chronic (31%) GVHD compared to PTCy and calcineurin inhibitors. (61) These findings suggest a potential trade-off between GVHD control and relapse risk when using sirolimus with PTCy. A recent randomized trial, BMT-CTN 1301, shed light on PTCy efficacy in the MAC setting with HLA-matched donors. (74) It compared three approaches: PTCy alone with BM, PTCy with CD34+-selected PBSC, and standard tacrolimus/methotrexate with BM. The primary goal was chronic GVHD/relapse-free survival. All three groups showed acceptable outcomes. However,

CD34+ selection in PBSC led to poorer survival due to higher NRM. Notably, PTCy alone achieved comparable results to the standard tacrolimus/methotrexate regimen.

Peripheral blood stem cells are currently the preferred stem cell source for PTCy based haploidentical alloHCT in the RIC setting.(75) The BMT-CTN1203 trial demonstrated a favorable hazard ratio for GRFS with PTCy/tacrolimus/mycophenolate mofetil compared to other GVHD prophylaxis regimens. Importantly, no differences in RI/POD or OS were observed. Building on these findings, the PROGRESS III trial investigated PTCy/tacrolimus/mycophenolate mofetil versus tacrolimus/methotrexate in the context of HLA-matched related or unrelated donors. (76) Patients were assigned in a 1:1 ratio to receive either PTCy/tacrolimus/mycophenolate mofetil (experimental arm) or the standard tacrolimus-methotrexate regimen (control arm). Both arms utilized HLA-matched related or matched or 7/8 mismatched unrelated donors with RIC/NMA conditioning and PBSC as graft source. The primary endpoint at one year was GRFS assessed by time-to-event analysis. Events included grade 3-4 acute GVHD, chronic GVHD requiring systemic immunosuppression, disease relapse/progression, and death from any cause. Multivariate Cox regression analysis revealed a statistically significant improvement in GRFS in the experimental prophylaxis group (n=214) compared to the standard prophylaxis group (n=217). The hazard ratio for events like severe acute/chronic GVHD, RI/POD, or death was 0.64 (95% CI: 0.49-0.83; p=0.001), favoring the experimental arm. At one-year, adjusted GRFS rates were 52.7% (95% CI: 45.8-59.2) and 34.9% (95% CI: 28.6-41.3) for experimental and standard prophylaxis, respectively. The experimental group also experienced lower rates of severe acute/chronic GVHD and a higher incidence of immunosuppression-free survival at one year. Notably, no significant differences were observed between groups in OS, disease-free survival, RI/POD, NRM, or engraftment. The prospective phase III HOVON-96 trial investigated cyclosporine with either PTCy or mycophenolate mofetil for GVHD prophylaxis in MRD and MUD PBSC transplants. (77) Notably, the PTCy arm showed lower rates of both acute and chronic GVHD. Similar findings emerged from a smaller phase II randomized study by Brissot et al., where PTCy/cyclosporine/mycophenolate mofetil was compared to the standard regimen of cyclosporine/methotrexate with ATG for MUD alloHCT using PBSC grafts and RIC/NMA. (78) At 6 months, no significant difference was observed in grade 2-4 acute

GVHD between the PTCy and ATG groups (35% vs. 24%, p = 0.24). Similarly, at 1-year, all-grade chronic GVHD rates were comparable (26% vs. 30%, p = 0.56). Both studies reported no significant differences in NRM, RI/POD, OS, GRFS or adverse events between the PTCy based and standard GVHD prophylaxis regimens. A large retrospective EBMT study (n=423) with acute leukemia patients confirmed the feasibility of PTCy based GVHD prophylaxis in the HLA-matched setting, regardless of BM or PBSC graft. (79) Notably, BM was the preferred source (74%) for patients receiving only PTCy. Conversely, PBSC was more common (74%) when PTCy was combined with one or two additional immunosuppressive medications. Both MAC and RIC were used. Interestingly, the only significant difference observed among the three groups (sole PTCy, PTCy + 1 drug, PTCy + 2 drugs) was a lower incidence of chronic GVHD when PTCy was used with just one additional immunosuppressive drug. Nagler et al. investigated PTCy monotherapy compared to cyclosporine/methotrexate for GVHD prophylaxis in MRD transplants for acute myeloid leukemia. (80) Peripheral blood stem cells were the predominant graft source in both arms. However, the PTCy group received less MAC conditioning. The sole statistically significant difference observed was a higher relapse rate in the PTCy group (HR 1.52; p=0.02). A recent phase 2 trial investigated the feasibility of alloHCT with PTCy/sirolimus/mycophenolate mofetil for HLA-mismatched unrelated donors (>=4/8 to 7/8 HLA matching). (81) Both MAC and RIC/NMA regimens (50% each) were used, with all patients receiving BM grafts. Encouragingly, the study demonstrated OS of 76% at one year, with no significant differences based on conditioning intensity or HLA match grade (7/8 vs. 4-6 matches). Acute GVHD rates were observed in 43% and 33% of patients receiving MAC and RIC/NMA regimens, respectively, at day 100. Chronic GVHD followed a similar trend, with rates of 36% and 18% at one year for MAC and RIC/NMA groups, respectively. Non-relapse mortality and RI/POD rates were comparable between MAC and RIC/NMA cohorts (8% vs. 10% and 30% vs. 23% at one year, respectively). Importantly, 48% of patients belonged to ethnic minorities, suggesting potential for expanded alloHCT access for underrepresented groups. Gaballa et al. reported acceptable outcomes in a phase 2 trial using RIC/NMA conditioning with BM grafts and PTCy/tacrolimus/mycophenolate mofetil for patients receiving MUD transplants with 9/10 HLA-matched donors (n=46). (82) At day 100, the rate of grade 2-4 acute GVHD was 33%. One-year NRM and OS were also promising (34% and 47%, respectively). Additionally, the prevalence of all-grade chronic GVHD at two years was 19%. Battipaglia et al. further explored PTCy efficacy by comparing MUD transplants with 9/10 HLA-

matched donor to haploidentical alloHCT in acute myeloid leukemia using the same prophylaxis. (83) Interestingly, their study found a paradoxical association between a lower frequency of HLA mismatches and decreased leukemia-free survival. However, no significant differences in OS were observed between the two groups. Pedraza et al. investigated a simplified GVHD prophylaxis regimen using PTCy and tacrolimus for both mismatched unrelated donor and MUD alloHCT in 109 patients. (84) The study observed similar rates of cumulative incidence for grade 2-4 acute GVHD (31% vs. 32%) and grade 3-4 acute GVHD (9% vs. 7%) between the mismatched unrelated donors and MUD groups. Importantly, no significant differences were found in chronic GVHD, OS, transplant-related mortality, or PFS between the two groups. These findings suggest that this PTCy-based regimen might be a viable option for mismatched unrelated donor alloHCT, potentially mitigating the negative impact of HLA disparity on transplant outcomes. Real-world data from a retrospective registry analysis sheds light on the comparative efficacy of PTCy versus ATG for GVHD prophylaxis in HLA-mismatched transplants in acute leukemia patients. (85) The analysis suggests a potential survival benefit associated with PTCy compared to ATG in the setting of mismatched unrelated donor transplants with 9/10 HLA-matched donors. However, this advantage seems to disappear when using matched related donors. (86) Paviglianiti et al. compared the use of PTCy based GVHD prophylaxis versus ATG based for lymphomas using a RIC in the setting of 9/10 MUD. (87) Despite a low number of patients and a heterogeneous population, no significant differences emerged from this study.

In conclusion, PTCy/tacrolimus/mycophenolate mofetil is superior to standard methotrexate-based GVHD prophylaxis in the setting of RIC/NMA and MRD/MUD/mismatched unrelated donor alloHCT thanks to the randomized PROGRESS III trial and the majority of retrospective studies. More data are needed to confirm such results in the myeloablative setting.

Study	**Type of conditioning**	**GVHD prophylaxis**	**Donor**	**Graft**	**Acute GVHD**	**Chronic GVHD**	**Overall survival**	**Commentary**
Luznik(68)	MAC (Bu/Cy)	PTCy day +3,+4	MRD (#78) MUD (#39)	BM	Grade 2-4 43%	9% and 11% for MRD and MUD,	55% at 2 years	First study to prove feasibility of PTCy in the HLA-matched setting

						respecti vely		
Mielcarek(71)	MAC (Bu/Flu,#25; TBI#18)	PTCy day +3,+4 and CSA	MRD (#12) MUD (#31)	PBSC	Grade 2-4 77%	16%	70% at 2 years	This study showed that when using MAC and PBSC, using only 2 immune suppressors can give higher acute GVHD rates
Carnevale-Schianca(72)	MAC (Bu/Flu + others)	PTCy day +3,+4 and tacrolimus and MMF	MRD (#10) MUD (#25)	PBSC	Grade 2-4 17%	7%	77% at 2 years	This study proved that maintaining 3 immune suppressive drugs, GVHD incidence can be maintained low even if using MAC and PBSC
Greco(73)	MAC (Treo/ Mel/Flu)	PTCy day +3,+4 and sirolimus and MMF (for MUD)	MRD (#15) MUD (#13)	PBSC	Grade 2-4 23%	13%	64% at 2-years (estimat ed)	This study showed that sirolimus can substitute tacrolimus with good results
Bolaños-Meade(75)	RIC (Flu/Cy/TBI)	PTCy day +3,+4 and tacrolimus and MMF	MRD (#29) MUD (#50) MMUD (#9)	PBSC	Grade 2-4 32%	39%	71% at 1 year	This study showed how PTCy/tacro/ MMF is the most effective GVHD strategy outside the CNI/MTX setting
Comparison studies of PT-Cy vs. standard GVHD prophylaxis in the settings of MRD, MUD or MMUD								
Battipaglia G (PT-Cy vs. ATG for MMUD donors)(85)	PTCy: MAC 50% ATG: MAC 50%	PTCy or ATG plus one or two immune suppressive drugs	PTCy = 93 patients ATG = 179 patients	PTCy: PBSC 91% ATG: PBSC 92%	Grade 3–4: 9% versus 19% (p = 0.04) in favor pf PTCy group	No differen ces	63% vs. 45% at 2 years (p < 0.5) in favor pf PT-Cy if patients in CR at	PTCy has less grade 3–4 acute GVHD and higher survival than ATG-based GVHD prophylaxis

							trasnplant	
Battipaglia G (PT-Cy vs. ATG for MRD donors)(86)	PTCy: MAC 59% ATG: MAC 48%	PTCy or ATG plus one or two immune suppressive drugs	MRD PTCy = 197 patients ATG = 1913 patients	PTCy: PBSC 70% ATG: PBSC 95%	No differences	All grade in 37% and 30% (p = 0.02) in favor of ATG	No differences	PTCy is not superior to ATG when used in the MRD setting
Paviglianiti A(87)	RIC	PTCy based (64)or ATG based (121)	MMUD (9/10 HLA matched)	PBSC only	No differences	No differences	No differences	PTCy is not superior to ATG when used in the MMUD setting
Boleaños-Meade(76)	RIC	PTCy/TAC/MMF (214) or TAC/MTX (217)	MRD (6/6) or MUD (7/8 and 8/8 HLA-matched)	PBSC only	Acute GVHD grade 3-4 at day +100 inferior in the T-Cy group (6.3% vs 14.7%)	All grade chronic GVHD at +1 year inferior in the T-Cy group (21.9% vs 35.1%)	No differences	Phase 3 study. GRFS was superior in the PTCy arm.
Brissot E(88)	RIC (Bu/Flu)	PTCy/CSA/MMF (45) or ATG/CSA/MMF (44)	MRD or MUD (10/10 HLA-matched)	PBSC only	No differences	No differences	No differences	Phase 2 randomized study. PTCy is as effective as ATG.
Comparison studies of haploidentical, MUD and MMUD in the PT-Cy setting								
Lorentino F (MMUD 9/10 vs. MUD 10/10 in PT-Cy) (89)	MMUD: MAC 56% MUD: MAC 53%	MMUD: PTCy + CNI + MMF 68% MUD: PT-Cy + CNI + MMF 49%	MMUD = 159 MUD = 305	MMUD: PBSC 88% MUD: PBSC 88%	No differences	No differences	No differences	PTCy abrogates the effect of 1 HLA mismatch in the setting of 9 of 10 or 10 of 10 unrelated donors
Gooptu M (Haploidentical vs. MUD) (90)	Haploidentical: MAC 41% MUD: MAC 34%	PTCy + CNI + MMF	Haploidentical = 2036 MUD = 284	Haploidentical: PBSC 63%	RIC cohort: lower acute GVHD	MAC cohort: lower chronic GVHD in	RIC cohort: 54% versus 67% in	MUD should be preferred over haploidentical donor when using PT-Cy

				MUD: PBSC 85%	in the MUD group	the MUD group	favor of haploidentical cohort	

Table 2. Selection of prospective studies using PT-Cy in the setting of HLA-matched donor alloHCT. GVHD=graft-versus-host-disease; MAC=myeloablative conditioning; PTCy=post-transplant cyclophosphamide; MRD=matched related donor; MUD= matched unrelated donor; BM=bone marrow; Bu=busulphan; Flu=fludarabine; TBI=total body irradiation= CSA=cyclosporine; PBSC=peripheral blood stem cell; MMF= mycophenolate mofetil; Treo=treosulpfan; MMUD=mismatched unrelated donor; CNI=calcineurin inhibitors.

Adapted from Mussetti, A.; Paviglianiti, A.; Parody, R.; Sureda, A. Is Post-Transplant Cyclophosphamide the New Methotrexate? (58)

Patient-related risk factors: prognostic scores

Allogeneic hematopoietic cell transplantation has been performed worldwide for over sixty years. It has been used to treat severe malignant and benign diseases. Hematologic tumors have always represented the main indications for this procedure, with acute myeloid leukemia being the first indication for alloHCT. Despite its well-known efficacy, its indication has always been associated with high mortality. For oncological diseases, relapse is the leading cause of death. However, NRM still accounts for 10-30% of deaths in patients treated with alloHCT and has several causes: toxicity of the conditioning regimen, infections, GVHD. (91) The causes of NRM are due to complex interactions between the patient, the disease, and transplant characteristics. Although a significant reduction in NRM has been reported in recent decades, it is crucial for the physician to estimate the risk that a specific patient has of dying after the procedure. Whenever the expected risk is considered higher than the risk of disease recurrence, alloHCT is generally contraindicated. Currently, the evaluation of a patient before transplantation consists of performing various functional tests and biochemical tests that, along with the patient's medical history and physical examination, help the physician exclude absolute contraindications to transplantation. After this, an estimation of transplant toxicity is made using prognostic scores. While prognostic scores predicting disease recurrence are based on disease characteristics, (92–95) those predicting NRM use a mixture of patient, transplant, and disease characteristics. Over the past 20 years, several prognostic NRM scales have been created and validated, which are integrated into daily clinical practice

(**Table 3**). Sorror et al.'s Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) is perhaps the most commonly used in clinical practice.(96) In general, no prognostic scale works better than the others. (97) However, all these tools share some common biases: nonspecific risk classification, created based on an outdated and/or small/monocentric patient population, exclusion of emerging types of alloHCT (e.g., haploidentical, use of PTCy), the use of a limited number of variables, or low accuracy in predicting mortality risk. Recently, different prognostic scores [Pretransplant assessment of mortality (PAM) (98), Disease-risk index (DRI), (92) Endothelial activation and stress index (EASIX), (99) EBMT/HCT-CI (100)] were compared in a cohort of 528 patients who had received alloHCT from the same institution. The discriminative ability of these scores in predicting OS and NRM has been shown to be low for all scores. In the future, personalized assessments of transplant candidates will be necessary to more precisely define mortality risk. Pending these new tools, it is essential to personalize the evaluation with a multidisciplinary team for all patients who have a high mortality score (any of those described) to ensure that clinically the patient has an excessively high risk of toxicity. Likewise, it will ensure that patients are not unjustifiably excluded from potentially curative therapy. The prognostic estimation of alloHCT outcomes is a fundamental part of the patient selection process for this procedure, influencing decision-making both for the healthcare team and for patients and their families. Currently, we have prognostic tools capable of providing predictive information based on the assessment of functional status, comorbidities, underlying disease characteristics, or biochemical parameters. Although there is no consensus on which index should be used over others, the determination of Karnofsky Performance Status and HCT-CI are the most prevalent within transplant centers.

Score, author, year	Prognostic score design	Predictive capacities
HCT-CI **Sorror ML et al.** **2005** (96)	Prognostic tool that includes the evaluation of 17 comorbidities scored according to their prognostic weight. The HCT-CI score ranges from 0 to 29 and is generally classified into the following 3 intervals: 0, 1 to 2, and 3+.	**OS, NRM**

Revised DRI **Armand P et al.** **2014** (92)	Scale that incorporates parameters related to the disease known as determinants of transplant success, such as initial diagnosis, disease status at allo-HSCT, and cytogenetic markers in myeloid malignancies. Patients are classified into 4 categories: low risk, intermediate risk, high risk, and very high risk of disease recurrence.	**RI/POD, OS**
EBMT Risk Score **Gratwohl A et al.** **2012** (100)	Composite index composed of five factors: patient age, disease stage, time since diagnosis, donor type, and donor-recipient gender combination, which increase the risk for an individual patient as the score increases from 0 (best) to 7 (worst) additively. Patients are classified into 5 risk groups based on the score obtained.	**OS, NRM**
Revised PAM score **Au BKC et al.** (98)	The composite score utilizes information about patient age, donor type, disease risk, patient and donor cytomegalovirus serology, and forced expiratory volume in 1 second. Based on a 50-point scoring system, patients are classified into 4 risk groups.	**OS,**
EASIX **Luft T et al.** **2017** (99)	Laboratory formula based on biomarkers defined as creatinine (mg/dl) x lactate dehydrogenase (LDH) (U/L) / platelets (x10e9/L). Considered a surrogate for endothelial activation. The optimal cutoff point to classify patients into a high-risk group is still under investigation.	**OS, NRM, post-transplant complicacitons**

Table 3. Prognostic scores used in hematopoietic cell transplants. HCT-CI=Hematopoietic Cell Transplant-Comorbidity Index; OS=overall survival; NRM=non-relapse mortality; DRI=Disease Risk Index; RI/POD=relapse incidence/progression of disease; PAM=Pretransplant Assessment of Mortality; EASIX=Endothelial Activation and Stress Index.

Geriatric scores

Improved outcomes in alloHCT have expanded the procedure's reach to older patients and those with significant comorbidities. This expansion has highlighted the need for more refined pre-transplant assessment methods. (101) Patient selection criteria for alloHCT focus on the

underlying hematological disease, patient's baseline condition, co-morbidities, and sometimes chronological age. However, these criteria do not fully consider important factors such as frailty.

Different definitions of frailty syndrome are present in literature. Generally, it can be considered as a clinical-biological syndrome characterised by reduced physiological reserves and diminished resilience to stressors and it is attributed to increasing age or cumulative wear and tear. Causes are different. (102) Aging represents the most common and natural cause. However, other factors are related to frailty. Among them: genetics; metabolic disorders like diabetes; environmental stressors such as chronic stress; poor lifestyle such as diet, smoking or lack of exercise; chronic disease like cancer, heart disease, respiratory syndromes. Frailty has been shown to be a strong predictor of morbidity and mortality in alloHCT patients. As a result, there is growing acceptance of incorporating frailty assessments into routine clinical practice for alloHCT candidates. (101,103,104) Frailty is relatively common in alloHCT candidates with a prevalence up to 25%. It is associated with an increased risk of toxicity and mortality. For these reasons, an assessment of frailty should be considered nowadays for all elderly patients or with a diminished performance status. Several tools are available today to perform such control. There are no specific treatments for frailty considering multifactorial pathogenesis. However, whenever a specific cause is identified (such as lack of exercise), specific interventions can be performed. Different workgroups have proposed different initiatives with the purpose of incorporating frailty assessment into the field of HCT. (105–111)

These scales, unlike a conventional medical assessment, also explore non-medical domains and emphasize the functional capacity and quality of life of people. A large part of the studies in this context incorporates the use of modified comprehensive geriatric assessments or have designed specific frailty scales based on the adaptation of certain geriatric scales, and conclude, homogeneously, that the presence of frailty infers negatively on the probability of developing post-transplant complications and is associated with a higher risk of mortality. However, despite the clinically relevant results obtained by these studies, most of the proposed methodologies require the intervention of qualified specialists, time, and material resources for their application, which will not necessarily be available in all transplant units.

In addition, many of these studies establish an age cut-off point for the performance of these scales, attributing the probability of presenting frailty to older patients. Despite these challenges, the benefits of incorporating frailty assessment into transplant practice exceed disadvantages.

Performing a frailty assessment has the following advantages:
- Improved risk stratification: frailty assessment can help identify patients at higher risk of complications and mortality after alloHCT.
- More informed decision-making: by considering frailty, clinicians can make more informed decisions about whether alloHCT is the best option for a particular patient.
- Better patient outcomes: by optimizing patient selection and treatment planning, frailty assessment can help improve alloHCT outcomes.

In the future, in order to improve patient selection, the following actions should be made development of standardized frailty assessment tools; validation of frailty assessment tools in alloHCT populations; identification of interventions to reduce frailty in alloHCT candidates; evaluation of the impact of frailty assessment on transplant outcomes.

In conclusion, it is important to emphasize that, to date, the assessment of frailty in the field of transplant has not followed a homogeneous diagnostic methodology, nor does it have sufficient evidence to limit its determination to cohorts of patients over a certain age cut-off point. However, numerous studies agree that frailty is multidimensional, dynamic, and potentially reversible with specific and appropriate interventions.

Current needs and future perspective to reduce transplant-related mortality

Considering the historical perspective presented here, a higher grade of treatment-related toxicity has always characterized alloHCT. While waiting for biggest scientific and medical discoveries which dramatically reduce toxicity, such as the introduction of newer antinfective drugs or GVHD prophylaxis strategies, it is fundamental to keep improving real-life practice in the alloHCT setting. Between the issues that can be improved through the interpretation of

currently available data, donor selection and a better identification of transplant candidates are fundamental. Regarding the correct choice of the most suitable donor in the PTCy era, it is fundamental to clarify if there are significant differences between MRD, MUD and haploidentical donors. In this sense, with our first work we compared the use of a MUD versus a haploidentical donor while using a PTCy GVHD prophylaxis. Regarding better patient identification, several prognostic factors have emerged during last years and there is not a score which considered all of these factors at the same time. In our second study, we built a newer prognostic model which, taking advantage of artificial intelligence methods, included all the major prognostic factors known today. Both studies were possible thanks to the use of international collaborations and the use of large dataset of patients retrieved from the CIBMTR and the EBMT.

HYPOTHESIS

Project 1"*Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas*"

We hypothesize that when using PTCy as GVHD prophylaxis, the use of a MUD is not superior to a haploidentical one

Project 2 "*Machine learning approach to estimate toxicity-related mortality following allogeneic hematopoietic cell transplantation*"

We hypothesize that the creation of a machine-learning prognostic risk score could be superior to current prognostic scores in defining OM and NRM

OBJECTIVES

Project 1"***Haploidentical versus matched unrelated donor transplants using post-transplant cyclophosphamide for lymphomas*****"**

Primary endpoint:

1) OS: events are death from any cause. Surviving patients are censored at time of last contact

Secondary endpoints:

2) Hematopoietic recovery: time to neutrophil recovery $\geq 0.5x10^9/l$; time to platelet recovery $\geq 20x10^9/L$

3) PFS: survival without progression. Patients are censored at time of last contact

4) acute GVHD: maximum overall grade of grade II-IV acute GVHD, we do not collect date of onset of acute GVHD

5) Relapse incidence: Time of relapse of the original malignancy post alloHCT

6) Non-relapse mortality (NRM): time to death without disease relapse

7) chronic GVHD: maximum extent of chronic GVHD, and time to cGVHD

8) Primary cause of death: according to Copelan algorithm, descriptive only

Project 2 "*Machine learning approach to estimate toxicity-related mortality following allogeneic hematopoietic cell transplantation*"

Primary endpoint:

1) showing that the new score is superior to classical ones in predicting NRM

Secondary endpoint:

2)showing that the new score is superior to classical ones in predicting OM

MATERIALS, METHODS, AND RESULTS

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Full Length Article
Allogeneic – Adult

Haploidentical Versus Matched Unrelated Donor Transplants Using Post-Transplantation Cyclophosphamide for Lymphomas

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A B S T R A C T

When using post-transplantation cyclophosphamide (PTCy) graft-versus-host disease (GVHD) prophylaxis for lymphoma patients, it is currently unknown whether a matched unrelated donor (MUD) or a haploidentical related donor is preferable if both are available. In this study we wanted to test whether using a haploidentical donor has the same results of a MUD. A total of 2140 adults (34% Center for International Blood and Marrow Transplant Research, 66% European Society for Blood and Marrow Transplantation registry) aged ≥18 years who received their first haploidentical hematopoietic cell transplantation (haplo-HCT) or MUD-HCT (8/8 match at HLA-loci A, B, C, and DRB1) for lymphoma using PTCy-based GVHD prophylaxis from 2010 to 2019 were retrospectively analyzed. The majority of both MUD and haploidentical HCTs received reduced intensity/nonmyeloablative conditioning (74% and 77%, respectively) and used a peripheral blood stem cell graft (91% and 60%, respectively) and a 3-drug GVHD prophylaxis (PTCy + calcineurin inhibitor + MMF in 54% and 90%, respectively). Haploidentical HCT has less favorable results versus MUD cohort in terms of overall mortality (hazard ratio [HR= = 1.69; 95% confidence interval [CI], 1.30-2.27; $P < .001$), progression-free survival (HR=1.39; 95% CI, 1.10-1.79; $P = .008$), nonrelapse mortality (HR = 1.93; 95% CI, 1.21-3.07; $P = .006$), platelet engraftment (HR = 0.69; 95% CI, 0.59-0.80; $P < .001$), acute grade 2-4 GVHD incidence (HR = 1.65; 95% CI, 1.28-2.14; $P < .001$), and chronic GVHD (HR = 1.79; 95% CI, 1.30-2.48, $P < .001$). No significant differences were observed in terms of relapse and

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neutrophil engraftment. Adjusting for propensity score yielded similar results. Whenever MUD is available in a timely manner, it should be preferred over a haploidentical donor when using PTCy-based GVHD prophylaxis for patients with lymphoma.

The use of post-transplantation cyclophosphamide (PTCy) based graft-versus-host disease (GVHD) prophylaxis rapidly expanded because of its promising results in the setting of haploidentical hematopoietic cell transplantation (haplo-HCT) [1]. Initial studies showed acceptable long-term survival and a strikingly low chronic GVHD incidence when using a reduced-intensity conditioning (RIC) and a marrow graft source for both myeloid and lymphoid malignancies [2–4]. Considering the promising and consistent results obtained in the haploidentical setting, retrospective comparisons between haplo-HCT with PTCy and matched-unrelated donor (MUD) HCT with standard GVHD prophylaxis (calcineurin inhibitor [CNI] + mycophenolate [MMF] or methotrexate with or without antithymocyte globulin [ATG]) were made in the setting of both myeloid and lymphoid malignancies [5–8]. Taking into consideration that international guidelines advise use of MUDs as the preferred donor type in the absence of an HLA-matched related donor [7], it is fundamental to understand the real impact of donor type when using PTCY-based GVHD prophylaxis. Although there are ongoing prospective trials to identify the best GVHD prophylaxis in the HLA-matched setting (e.g., PROGRESS 3 trial, NCT03959241), it is difficult to conduct randomized trials based on donor type. Recently, Gooptu et al. [8] performed a comparison between MUD and haploidentical donor transplantation, both using PTCy GVHD prophylaxis, for myeloid diseases. That study demonstrated a substantial survival benefit with MUDs for allogeneic HCT with reduced-intensity conditioning regimen. The aim of our study was to explore the same question in lymphomas.

MATERIALS AND METHODS

Data sources

The study was performed through collaboration between the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) as described elsewhere [9].

Patients

Included in this analysis are adult (≥18 years) patients with Hodgkin (HL) or non-Hodgkin lymphoma (NHL) treated with haplo-HCT or MUD-HCT using PTCy-based GVHD prophylaxis between 2010 and 2019 and reported to either the CIBMTR or EBMT. Recipients of haplo-HCT were mismatched at 2 or more HLA loci, whereas MUD transplants were matched at the allele level at HLA-A, -B, -C, and -DRB1 (8/8). GVHD prophylaxis in both groups included PTCy-based regimens, most commonly in combination with CNI + MMF. Both peripheral blood and bone marrow grafts were included. Myeloablative and non-myeloablative/reduced intensity conditioning were included.

Definitions

The intensity of conditioning regimens was determined using consensus criteria [10]. Response to last line of therapy before allo-HCT was defined as per Lugano criteria [11].

Study Endpoints

The primary endpoint overall survival (OS) and secondary endpoints non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS), neutrophil and platelet recovery, acute GVHD and chronic GVHD were calculated using standard criteria [12].

Statistical analysis

The haplo-HCT cohort was compared against the MUD-HCT cohort. Probabilities of PFS and OS were calculated as described previously [13]. Cumulative incidences of NRM, lymphoma progression/relapse, and hematopoietic recovery were calculated to accommodate for competing risks [14]. The primary analysis evaluated associations among patient-, disease-, and transplantation-related variables and outcomes of interest using Cox proportional hazards regression. Backward elimination was used to identify covariates associated with outcomes. Covariates with a $P < .05$ were retained in the models. To adjust for association testing of multiple endpoints, a statistically significant difference was considered when $P < .01$. The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were adjusted via stratification in the Cox regression model. Interactions between the main effect and significant covariates were examined. Center effect was adjusted as clusters using the Generalized estimating equation (GEE) approach for all the endpoints [15]. Relative risks were expressed as hazard ratios (HR). Variables considered in the multivariate analyses are shown in Supplementary File 1 of the Supplemental Appendix. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Because of concerns about the potential imbalance of significant risk factors between the haplo-HCT and MUD-HCT cohorts, a sensitivity analysis based on propensity score was also conducted (Supplementary File 2). The propensity score was based on disease, disease stage, donor/recipient cytomegalovirus (CMV) status, HCT-CI, Karnofsky performance status, registry (EBMT versus CIBMTR), patient age, and donor age. Because the maximum unrelated donor age was 55 years old, these additional analyses, including calculation of propensity scores, excluded 260 patients receiving transplants from haploidentical donors older than 55 years old.

RESULTS

Baseline Characteristics

The baseline patient-, disease-, and transplantation-related characteristics are shown in Table 1. Lymphoma subtypes in haploidentical transplant recipients were 44% HL and 56% NHL; in MUD recipients they were 28% HL and 72% NHL ($P < .001$). GVHD prophylaxis consisted of PTCy + CNI + MMF in 90% of the haploidentical group and 54% of the MUD group ($P < .001$). The graft source was peripheral blood in 60% (n = 1089) of haplo-HCT and 91% (n = 283) of MUD transplantations ($P < .001$). The donor age was <40 in 51% (n = 927) of haplo-HCT and 76% (n = 236) of MUD ($P < .001$). The maximum MUD age was 55 years.

OS

The estimated 2-year OS rates were 63% (95% confidence interval [CI], 61-66) and 73% (95% CI, 67-79) in the haplo-HCT and MUD groups, respectively (overall $P = .007$) (Table 2, Figure 1A). In multivariate analysis (Table 3, Figure 2), haplo-HCT was associated with higher overall mortality (inverse of OS) compared to MUD-HCT, (HR = 1.69; 95% CI, 1.30-2.27; $P < .001$). Independent of donor type, pre-HCT disease status being PR or chemoresistant (overall $P < .001$), HCT-CI ≥3 (HR = 1.47; 95% CI, 1.17-1.86) and Karnofsky performance score <90 (HR = 1.46; 95% CI, 1.13-1.88; $P = .004$) were associated with poorer survival (Supplementary File 1)

PFS

The estimated 2-year PFS was 53% (95% CI, 50-55) and 63% (95% CI, 57-69) in the haplo-HCT and MUD groups, respectively (overall $P = .004$) (Table 2, Figure 1B). Multivariate analysis (Table 3, Figure 2) showed that haplo-HCT was associated with higher rates of progression or death (inverse of PFS) compared to MUD-HCT, (HR = 1.39; 95% CI, 1.10-1.79; $P = .008$). Independent of donor type, pre-HCT disease status being PR or chemoresistant (overall $P < .001$), and Karnofsky performance score

Table 1
Baseline Characteristics of CIBMTR and EBMT Cohorts of Lymphoma Patients Undergoing Haploidentical Related Donor or 8/8 Matched Unrelated Donor Transplantation[*,†]

Variable	Haploidentical	Matched Unrelated	*P* Value[‡]
Number of recipients	1830	310	
Number of centers	277	103	
Recipient age at transplantation			<0.001
18-29 years	429 (23%)	45 (15%)	
30-39 years	316 (17%)	48 (15%)	
40-49 years	298 (16%)	40 (13%)	
50-59 years	443 (24%)	89 (29%)	
60 years and older	344 (19%)	88 (28%)	
Median (Range)	46 (18-71)	53 (19-71)	<0.001
Sex			0.07
Male	1169 (64%)	214 (69%)	
Female	660 (36%)	95 (31%)	
Missing	1 (<1%)	1 (<1%)	
Karnofsky performance score			0.09
90-100	1282 (70%)	200 (65%)	
10-80	497 (27%)	103 (33%)	
Missing	51 (3%)	7 (2%)	
HCT-CI			<0.001
≤2	1050 (57%)	157 (51)	
>2	362 (20%)	94 (30)	
Missing	418 (23%)	59 (19)	
Lymphoma subtype			<0.001
Follicular Lymphoma	137 (7%)	31 (10)	
DLBCL	447 (24%)	75 (24)	
Mantle cell Lymphoma	178 (10%)	53 (17)	
Classical Hodgkin lymphoma	805 (44%)	86 (28)	
T-cell lymphoma	263 (14%)	65 (21)	
NHL Disease status prior to HCT			0.54
Complete remission	535 (52%)	122 (54)	
Partial remission	317 (31%)	61 (27)	
Chemoresistant	173 (17%)	41 (18)	
HD Disease status before HCT			0.07
Complete remission	397 (49%)	52 (60)	
Partial remission	264 (33%)	18 (21)	
Chemoresistant	144 (18%)	16 (19)	
Prior auto-HCT			0.05
No	736 (40%)	143 (46)	
Yes	1094 (60%)	167 (54)	
Graft type			<0.001
Marrow	741 (40%)	27 (9)	
PBSC	1089 (60%)	283 (91)	
Conditioning regimen intensity			0.23
Myeloablative	415 (23%)	80 (26)	
Non-myeloablative/RIC	1415 (77%)	230 (74)	
GVHD prophylaxis			<0.001
PTCy + CNI + MMF	1647 (90%)	167 (54)	
PTCy + others[c]	183 (10%)	143 (46)	
Time from diagnosis to HCT (mo)			
Median (Range)	29 (3-421)	32 (3-369)	0.88
N Eval	1822	309	
Donor age			<0.001
Less than 20 years	112 (6%)	13 (4)	
20-29 years	392 (21%)	155 (50)	
30-39 years	423 (23%)	68 (22)	
40-49 years	307 (17%)	30 (10)	
50+ years	402 (22%)	7 (2)	

(*continued*)

Table 1 (*Continued*)

Variable	Haploidentical	Matched Unrelated	*P* Value[†]
Missing	194 (11%)	37 (12)	
Median (Range)	37 (12-76)	28 (18-55)	<0.001
Donor/recipient sex match			<0.001
Male-to-male	706 (39%)	166 (54)	
Male-to-female	341 (19%)	55 (18)	
Female-to-male	461 (25%)	44 (14)	
Female-to-female	317 (17%)	39 (13)	
Missing	5 (<1%)	6 (2)	
Donor/recipient CMV match status			<0.001
Donor +/ recipient +	843 (46%)	95 (31)	
Donor +/ recipient –	228 (12%)	36 (12)	
Donor – / recipient +	310 (17%)	77 (25)	
Donor – / recipient –	406 (22%)	94 (30)	
Missing	43 (2%)	8 (3)	
Year of transplant			0.002
2010-2014	529 (29%)	63 (20)	
2015-2019	1301 (71%)	247 (80)	
Follow-up among survivors, Months			
N Eval	1146	231	
Median (25th-75th quartiles)	33 (14-55)	21 (12-35)	<0.001

* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables
† Evaluable patients in haploidentical group = 1146 and MUD group = 231.
‡ PTCy + others: CNI only, sirolimus, methotrexate.

<90 (HR = 1.40; 95% CI, 1.17-1.68; $P < .001$) were associated with poorer survival.

Relapse and NRM

The cumulative incidences of relapse at 2 years were 27% (95% CI, 25-29) and 22% (95% CI, 17-27) in the haploidentical and MUD groups, respectively (overall $P = .213$; Table 2, Figure 1D). Multivariate analysis (Table 3, Figure 2) showed no significant difference in the risk of relapse/progression with haplo-HCT versus MUD (HR = 1.04; 95% CI, 0.78-1.38; $P = .805$). Independent of donor type, HCT done between 2017 to 2019 (compared to 2010–2013 and 2014–2016) was associated with a lower risk for lymphoma relapse, (HR = 0.70; 95% CI, 0.56-0.88; $P < .001$) (Supplementary File 1).

Among recipients of haplo-HCT, the 1-year NRM was 18% (95% CI, 16-20) compared with 12% (95% CI, 8-16) in MUD recipients. The corresponding 2-year NRM was 21% (95% CI, 19-23) and 15% (95% CI, 10-19), respectively (overall $P = .024$; Table 2, Figure 1C). Multivariate analysis showed a significantly higher risk of TRM with haplo-HCT versus MUD HCT (HR = 1.93; 95% CI, 1.21-3.07; $P = .006$). Independent of donor type, older donor age (cutoff for statistical significance ≥50, $P = .007$) and older recipient age ≥50 (overall $P < .001$) were associated with inferior NRM.

Hematopoietic Recovery

The cumulative incidence of neutrophil recovery at day 28 was 90% (95% CI, 89-92) in the haploidentical group compared with 93% (95% CI, 90-96) in the MUD group (overall $P < .001$). The day-28 and day-100 cumulative incidences of platelet recovery in similar order were 54% (95% CI, 51-56) and 66% (95% CI, 60-71) and 86% (95% CI, 84-87) and 92% (95% CI, 88-95) (overall $P < .001$; Table 2). Multivariate analysis (Table 3, Figure 2) revealed a slower rate of platelet engraftment in haploidentical compared to MUD transplant recipients (HR = 0.69; 95% CI, 0.59-0.80; $P < .001$); rates of neutrophil recovery were not statistically different (HR = 0.82; 95% CI, 0.68-0.97, $P = .025$).

Independent of donor type, sex mismatched transplants from female donor to male recipient (HR = 0.86; 95% CI, 0.77-0.95; $P = .003$) and recipient age ≥60 (overall $P < .001$) were associated with poorer neutrophil recovery (Supplementary File 1). Similarly, platelet recovery was negatively associated with chemoresistant disease status (HR = 0.81; 95% CI, 0.71-0.92; $P = .001$), HCT-CI score ≥2 (overall $P \leq .001$), time from diagnosis to transplant of 6 to 12 months (HR = 0.61; 95% CI, 0.44-0.84; $P = .003$) and recipient age ≥40 (overall $P < .001$), whereas donor-positive/patient-negative CMV serological status was associated with better platelet recovery (HR = 1.27; 95% CI, 1.09-1.47; $P = .002$) (Supplementary File 1).

Acute and Chronic GVHD

Univariate analysis showed the cumulative incidence of grade II-IV acute GVHD at day 100 (Table 2) in the haplo-HCT cohort was 33% (95% CI, 31-35) compared with 24% (95% CI, 20-30) in the MUD group, (overall $P = .004$). The corresponding rates of grade III-IV acute GVHD were 10% (95% CI, 8-11) and 5% (95% CI, 3-8), overall $P = .018$. Multivariate analysis (Table 3) showed a higher risk of both grade II-IV acute GVHD (HR = 1.65; 95% CI, 1.28-2.14; $P < .001$) and grade III-IV acute GVHD (HR = 2.04; 95% CI, 1.28-3.25; $P = .003$) in haploidentical compared to MUD transplant recipients.

The cumulative incidences of chronic GVHD at 1 year (Table 2) in the haplo-HCT and MUD groups were 24% (95% CI, 22-26) and 17% (95% CI, 13-22) respectively, overall $P = .124$. However, multivariate analysis indicated the risk of chronic GVHD was significantly higher after haploidentical transplantation (HR = 1.79; 95% CI, 1.30-2.48; $P < .001$) relative to MUD allo-HCT (Table 3, Figure 2). In the haplo-HCT group, a

Table 2
Univariate Analysis of Patient Outcomes by Donor Type

Outcomes	Haploidentical		Matched Unrelated		Overall *P* Value
	N	Prob (95% CI)	N	Prob (95% CI)	
Neutrophil engraftment	1753		292		<.001
28-day		90% (89%-92%)		93% (90%-96%)	
100-day		96% (95%-97%)		98% (96%-99%)	
Platelet recovery	1653		259		<.001
28-day		54% (51%-56%)		66% (60%-71%)	
100-day		86% (84%-87%)		92% (88%-95%)	
Acute GVHD II-IV	1690		279		.004
100-day		33% (31%-35%)		24% (20%-30%)	
Acute GVHD III-IV	1707		286		.018
100-day		10% (8%-11%)		5% (3%-8%)	
Chronic GVHD	1717		277		.124
6 months		14% (12%-16%)		10% (7%-14%)	
1-year		24% (22%-26%)		17% (13%-22%)	
2-year		28% (26%-30%)		23% (18%-29%)	
Relapse	1728		293		.213
100-day		9% (7%-10%)		7% (5%-10%)	
1-year		21% (20%-23%)		20% (15%-25%)	
2-year		27% (25%-29%)		22% (17%-27%)	
Non-relapse mortality	1728		293		.024
100-day		9% (7%-10%)		6% (4%-10%)	
1-year		18% (16%-20%)		12% (8%-16%)	
2-year		21% (19%-23%)		15% (10%-19%)	
Progression-free survival	1728		293		.004
100-day		83% (81%-85%)		86% (82%-90%)	
1-year		61% (58%-63%)		69% (63%-74%)	
2-year		53% (50%-55%)		63% (57%-69%)	
Overall Survival	1830		310		.007
1-year		72% (70%-74%)		80% (75%-85%)	
2-year		63% (61%-66%)		73% (67%-79%)	

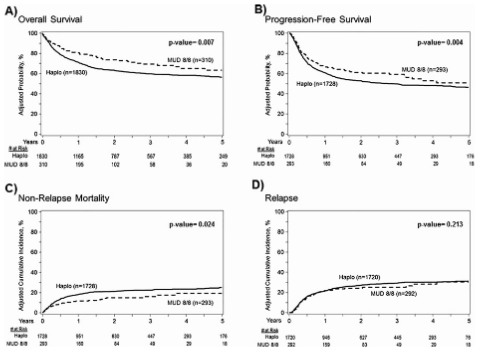

Figure 1. Kaplan-Meier estimates and cumulative incidence. (A) The 2-year OS was 63% (95% CI, 61%-66%) and 73% (95% CI, 67%-79%) in the haploidentical and matched unrelated groups, *P* = .007. (B) The 2-year PFS was 53% (95% CI, 50%-55%) and 63% (95% CI, 57%-69%) in the haploidentical and matched unrelated groups, *P* = .004. (C) The 2-year NRM was 21% (95% CI, 19%-23%) and 15% (95% CI, 10%-19%) in the haploidentical and matched unrelated groups, *P* = .024. (D) Relapse: 2-year risk of lymphoma relapse was 27% (95% CI, 25%-29%) and 22% (95% CI, 17%-27%) in the haploidentical and matched unrelated groups, *P* = .21.

peripheral blood stem cells graft was associated to higher risk of acute grade 2-4 GVHD, acute grade 3-4 GVHD, and chronic GVHD.

Sensitivity analysis for the primary outcome of overall mortality: Inverse Probability Treatment Weighting Regression Using Propensity Score (PS) Weighting and Propensity Score Matching Analysis

Considering the heterogeneity of the study population, particularly with regard to patient and donor age, 2 sensitivity analyses using propensity scores on a restricted subcohort of patients receiving transplants from donors age ≤55 years old were conducted. The PS was based on disease, disease stage, donor CMV status, HCT-CI, Karnofsky performance status, registry, patient age, and donor age (Supplementary File 2). Both sensitivity analyses confirmed multivariate results, whether patient age and donor age were considered as continuous or categorical variables in the PS modeling. Considering ages as continuous variables, the Inverse Probability Treatment Weighting weighted Cox model for overall mortality (1 –OS) with haploidentical versus MUD HCT show a HR of 1.38 (95% CI, 1.03-1.85; *P* = .03). Considering age as categorical variables, the HR was 1.36 (95% CI, 1.01-1.83; *P* = .04).

Table 3
Multivariate Analysis of Transplant Outcomes by Donor Type

Outcome by Donor Type	Evaluable	Events	HR (95% CI)	*P* Value
Neutrophil engraftment*				
Haploidentical	1753	1681	0.82 (0.68-0.97)	.025
Matched unrelated	292	288	1.00	
Platelet recovery†				
Haploidentical	1645	1423	0.69 (0.59-0.80)	<.001
Matched unrelated	258	243	1.00	
Acute GVHD II-IV‡				
Haploidentical	1690	590	1.65 (1.28-2.14)	<.001
Matched unrelated	279	71	1.00	
Acute GVHD III-IV§				
Haploidentical	1707	179	2.04 (1.28 – 3.25)	.003
Matched unrelated	286	17	1.00	
cGVHD‖				
Haploidentical	1721	464	1.79 (1.30-2.48)	<.001
Matched unrelated	277	58	1.00	
Relapse¶				
Haploidentical	1720	465	1.04 (0.78-1.38)	.805
Matched unrelated	292	63	1.00	
Non-relapse mortality#				
Haploidentical	1728	367	1.93 (1.21-3.07)	.006
Matched unrelated	293	41	1.00	
Progression or death**				
Haploidentical	1728	838	1.39 (1.10-1.79)	.008
Matched unrelated	294	104	1.00	
Overall mortality††				
Haploidentical	1830	684	1.69 (1.30-2.27)	<.001
Matched unrelated	310	79	1.00	

* Adjusted by patient age, HCT CI, sex match; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
† Adjusted by patient age, HCT CI, CMV match, disease stage, time from diagnosis to transplant; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
‡ Adjusted by donor age, HCT CI; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
§ Adjusted by previous auto HCT; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
‖ Adjusted by previous auto HCT; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
¶ Adjusted by year of transplant; stratified by disease stage, time from diagnosis to transplant, population resources, GVHD prophylaxis, graft type and conditioning regimen.
# Adjusted by patient age, disease stage, donor age, CMV match, Karnofsky score; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.
** Inverse of progression-free survival; adjusted by disease stage, CMV match; stratified by disease type, donor age, population resources, GVHD prophylaxis, graft type and conditioning regimen.
†† Inverse of overall survival; adjusted by patient age, disease stage, HCT CI, CMV match, Karnofsky score; stratified by disease type, donor age, population resources, GVHD prophylaxis, graft type and conditioning regimen.

A propensity score matched-pair analysis was also performed. We were able to match 273 pairs. Treating age as a continuous variable, there was no difference in propensity scores (P = .96), patient age (P = .48), or donor age (P = .26) between haplo-HCT and MUD HCT recipients in the matched cohort. The HR for overall mortality with haploidentical versus MUD was 1.49 (95% CI, 1.09-2.04), P = .012. Considering age as a categorical variable, there was again no difference in propensity scores or donor or patient age between haploidentical and HCT recipients in the matched cohort, and the HR for mortality was 1.58 (95% CI, 1.16-2.16; $P < .01$)

Causes of Death

With a median follow-up of 33 months (range 0-123) in the haplo-HCT and 21 months (range 0-108) in the MUD group, numbers of deaths in both groups at last follow-up were 684 and 79, respectively. As reported by the treating institution, lymphoma relapse/progression was the cause of death in 244 (36%) and 29 (37%) of patients in the haplo-HCT and MUD recipients, respectively, making it the most common cause of death in either group (Table 4). Other leading causes of deaths were infection followed by GVHD in both haplo-HCT and MUD recipients. It should be noted that cause of death data was missing in 23 (3%) of haplo-HCT and 5 (6%) of MUD patients.

DISCUSSION

The advent and widespread use of PTCy-based GVHD prophylaxis to successfully perform HLA-mismatched transplantation has made haploidentical donors an acceptable graft source that is rapidly available for the vast majority of patients, even those under-represented in international donor registries [16]. Nevertheless, the existing evidence did not allow us to know whether this is the best approach if using PTCy-based GVHD prophylaxis for MUD HCT.

In the current study, where all transplantations were done using the PTCy platform, the use of MUDs was associated with a significant advantage in OS. This effect was explained by lower NRM and GVHD incidences. No significant differences

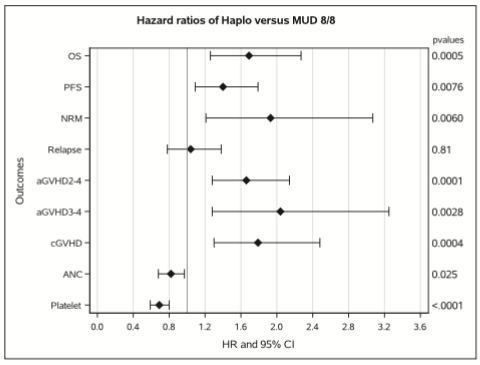

Figure 2. Forest plot showing the results of multivariate analysis of patients with lymphomas undergoing haploidentical donor versus matched unrelated donor allogeneic transplantation using post-transplantation cyclophosphamide-based GVHD prophylaxis. HR to the right of 1.0 favor MUD for all outcomes except ANC and platelets. For ANC and platelets, HR to the left of 1.0 favor MUD.

were observed in relapse. These results are in line with a recent study from Gooptu et al. [8], where a survival advantage of MUDs over haploidentical donors in the myeloid RIC setting was explained by a higher NRM, driven in part by more frequent acute GVHD. In our study, almost 70% of patients in both cohorts received RIC, which is expected in a lymphoma cohort. Compared to the Gooptu study, we also observed an association between a higher chronic GVHD incidence and the use of a haploidentical donor. A second difference between the 2 groups was the shorter platelet engraftment time of the MUD cohort. This could be explained by the more prevalent use of peripheral blood stem cell graft in this group. This difference has been previously documented both in the use of standard CNI-based GVHD prophylaxis and HLA-matched donors [17] and in the haploidentical setting with PTCy [18]. However, other studies reported in literature are describing different results when comparing haplo-HCT to MUD in lymphomas. In a recent metanalysis by Gagelmann et al. [19], showed that haplo-HCT with PTCy had increased relapse than MUD for lymphoma patients. However, in that large metanalysis, GVHD prophylaxis for the MUD cohort was ATG-based in most cases.

This analysis also shows that PTCy can be used for MUD HCT. We previously demonstrated 3-year OS rates of 62% and 50% for MUDs with standard calcineurin inhibitor GVHD prophylaxis, without or with ATG, respectively [6]. The 72% 2-year OS after MUD HCT cohort in the current study, using PTCy, compares well with these previously published results. The same is true for relapse incidence (28% and 36% at 3 years versus 22% at 2 years), NRM (13% and 20% versus 12% at 1 year), PFS (49% and 28% at 3 years versus 63% at 2 years), grade 2-4 acute GVHD (40% and 49% versus 24% at day +100) and chronic GVHD (51% and 33% versus 17% at 1 year). Prospective trials, including the CTN PROGRESS 3 study (NCT03959241), are addressing this question in a randomized fashion. Although the use of PTCy should not yet be considered standard, a recent prospective phase 2 study from Shaw et al. shows how such a platform could be safely used for HLA mismatched unrelated donor HCT (with bone marrow graft) [20], making it an attractive platform to expand the donor pool to races and ethnicities underrepresented in donor registries. However, other differences such as infections incidence (e.g., viral reactivations, fungal infections) should also be considered while comparing different GVHD prophylaxis [21]. In our study, causes of death related to infectious complications were similar between the two types of donor. This was in line with previous reports [22].

Table 4
Causes of Death

Cause of Death	Haploidentical*	Matched Unrelated†
Primary Disease	244 (36%)	29 (37%)
GVHD	95 (14%)	9 (11%)
Infection	197 (29%)	22 (28%)
Other Causes	125 (18%)	14 (18%)
Missing	23 (3%)	5 (6%)

* No. of deaths = 684.
† No. of deaths = 79.

A third significant observation in our study is related to the HL subset analysis. No significant differences between haploidentical or MUD donors were confirmed in the HL population (Supplementary File 3). Probably, the low number of patients and short follow-up of the MUD cohort did not allow the study to have sufficient statistical power.

This study has some limitations. The inclusion of PTCy as GVHD prophylaxis platform in the MUD setting is quite recent. The number of reported patients is limited, and this fact might compromise the statistical power to detect small differences in outcomes. To overcome this issue, a joint study between CIBMTR and EBMT, the 2 largest HCT registries in the world, was made. Second, we do not know how centers performed donor selection. It is possible that a few centers preferred haploidentical donor over MUD donor based on institutional preference or because of time restrictions whereas others deferred use of a haploidentical donor until a MUD search was unsuccessful, which could introduce bias. However, we believe that a prospective randomized study between MUD and haploidentical donors would be extremely difficult to conduct because both types of donors may not be available for all patients. Another issue is the heterogeneity of the study population in terms of donor registry, GVHD prophylaxis, graft source, conditioning regimen and donor age. All these factors were included and adjusted for in the multivariate analyses. Results were also confirmed independently in two sensitivity analyses that incorporated propensity scores to further adjust for population differences. Regarding the use of different GVHD prophylaxis, we can observe that the MUD cohort received more heterogeneous prophylaxis regimens instead of the classic PTCy + CNI + MMF. Specifically, in the MUD cohort there was a higher percentage of patients who received a 2-drug (PTCy + CNI) instead of classic 3-drug GVHD prophylaxis (0.7% versus <0.1%). We know from a previous study from the EBMT that a 3-drug PTCy-based GVHD prophylaxis has a better GVHD and relapse-free survival [23]. Despite this, the MUD cohort had a lower GVHD incidence, possibly suggesting that a 2-drug PTCy-based GVHD prophylaxis can be sufficient in this setting. This has been reported in a recent study by Mehta and colleagues [24]. Of note, in a recent prospective randomized study made in HLA-identical donors, the sole use of PTCy without additional drugs had same results that standard CNI-based GVHD prophylaxis [25]. Another critique could be related to the higher use of BM graft in the haploidentical cohort. To compensate for different use of graft sources, we performed an analysis restricted to peripheral blood stem cell population (Supplementary File 4) confirming general results. Also, the study population is quite heterogeneous in terms of disease type between the two groups. This could limit the analysis of the graft-versus-lymphoma effect, which is different depending on lymphoma subtype. Finally, median donor

age was higher in the haploidentical group (37 years versus 29 years). Adjustments for age were performed in 2 separate analyses. In addition, in a recent retrospective study from Perales et al. [26] comparing MUD with standard GVHD prophylaxis versus haplo-HCT with PTCy for acute myeloid leukemia, donor age had no significant impact on survival. The same results were confirmed on a large retrospective analysis on haplo-HCT with PTCy where donor age did adversely affect survival despite being associated with higher acute GVHD and NRM incidence. The latter was counterbalanced by less relapse [27]. Prospective data could help to further address this question.

In conclusion, our results suggest that use of a MUD over a haploidentical donor when using PTCy-based GVHD prophylaxis could be preferable for non-Hodgkin lymphoma patients. The data do not support favoring a haploidentical donor if a MUD is available in a timely manner. MUD donors are unfortunately less of an option for the majority of patients/recipients of non-European Caucasian descent who either do not have quick access to an 8/8 MUD donor or have no 8/8 MUD donor prospect. For this large group, haploidentical transplantations result in acceptable outcomes for this high-risk disease population. Moreover, PTCy seems to be a valid alternative to standard CNI-based GVHD prophylaxis for MUD HCT. Clinical differences between the MUD and haploidentical cohorts such as a different use of graft sources (bone marrow was mostly used in the haploidentical cohort) or type of registry (CIBMTR versus EBMT) could have biased these results, and prospective trials are awaited in this setting.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2022.11.028.

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Artificial intelligence methods to estimate overall mortality and non-relapse mortality following allogeneic HCT in the modern era: an EBMT-TCWP study

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Allogeneic haematopoietic cell transplantation (alloHCT) has curative potential counterbalanced by its toxicity. Prognostic scores fail to include current era patients and alternative donors. We examined adult patients from the EBMT registry who underwent alloHCT between 2010 and 2019 for oncohaematological disease. Our primary objective was to develop a new prognostic score for overall mortality (OM), with a secondary objective of predicting non-relapse mortality (NRM) using the OM score. AI techniques were employed. The model for OM was trained, optimized, and validated using 70%, 15%, and 15% of the data set, respectively. The top models, "gradient boosting" for OM (AUC = 0.64) and "elasticnet" for NRM (AUC = 0.62), were selected. The analysis included 33,927 patients. In the final prognostic model, patients with the lowest score had a 2-year OM and NRM of 18 and 13%, respectively, while those with the highest score had a 2-year OM and NRM of 82 and 93%, respectively. The results were consistent in the subset of the haploidentical cohort ($n = 4386$). Our score effectively stratifies the risk of OM and NRM in the current era but do not significantly improve mortality prediction. Future prognostic scores can benefit from identifying biological or dynamic markers post alloHCT.

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INTRODUCTION

Allogeneic haematopoietic cell transplantation (alloHCT) has been performed worldwide for more than 60 years [1] in the treatment of serious malignant and benign diseases [2, 3]. Despite its well-known efficacy, it has always been associated with high mortality. Non-relapse mortality (NRM) is responsible for 10–30% of deaths after alloHCT [4]. These are due to the toxicity of the conditioning regimen, infections, and graft-versus-host disease (GVHD), and are

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usually determined by complex interactions between patient, disease, and transplant characteristics. It is crucial for the clinicians to estimate each patient's risk of dying following alloHCT. Transplant-related toxicity is usually estimated using prognostic scores. While scores that predict disease relapse rely on disease characteristics [5–7], those predicting NRM use a combination of patient-, transplant- and disease-related characteristics. Several NRM prognostic scores have been created and validated in the last 20 years [8–15]. The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) developed by Sorror et al. is perhaps the most commonly used in clinical practice [8]. In general, no prognostic scoring system performs better than the others [16]. However, many of these scores share some common biases: non-specific classification of risk, created with an old and/or small/single-centre patient population, exclusion of emerging alloHCT types (e.g. haploidentical, post-transplant cyclophosphamide use), use of a limited number of variables, and low score accuracy. To overcome such problems, we took a recent large cohort of patients from the European Society for Blood and Marrow Transplantation (EBMT) and applied modern artificial intelligence (AI) methods with the aim of improving the prediction of mortality and NRM after alloHCT.

PATIENTS AND METHODS

Data sources and study design

The study was performed using the EBMT database. The EBMT is a voluntary working group of more than 600 transplant centres that are required to report regular follow-ups on all consecutive stem cell transplants. Audits are routinely performed to determine the accuracy of the data. The study was planned and approved by the Transplant Complications Working Party of the EBMT. EBMT centres commit to obtaining informed consent according to local regulations applicable at the time of transplantation in order to report pseudonymized data to the EBMT. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. For the purpose of this study, all necessary data were collected according to EBMT guidelines, using the EBMT Minimum Essential Data (Med) forms.

Patients

Eligibility criteria included adult patients (≥ 18 years old) who received a first alloHCT for acute myeloid and lymphoid leukemias, Hodgkin and non-Hodgkin lymphomas, multiple myeloma and myelodysplastic syndromes. Graft sources were bone marrow and peripheral blood stem cells. Myeloablative and non-myeloablative/reduced intensity conditioning regimens were used. Any disease status at the time of transplant was considered. Data was collected for transplants performed between January 2010 and December 2019. Graft-versus-host-disease (GVHD) prophylaxis was methotrexate-based, post-transplant cyclophosphamide (PTCy)-based, or ex-vivo T cell depletion (CD34+ selection). Use of in-vivo T cell depletion with anti-thymocyte globulin (ATG) and/or alemtuzumab was also considered. In order to create a prognostic score, we collected all pre-transplant clinical factors with a well-known effect on mortality outcomes. Patient (age, sex, Karnofsky score, presence of significant comorbidities, total number of comorbidities, cytomegalovirus [CMV] serostatus), donor (sex, CMV serostatus, donor type), transplant (graft type, conditioning intensity, GVHD prophylaxis), and disease (disease risk index, type of disease, disease status at transplant) characteristics were also recorded.

Definitions

The intensity of the conditioning regimens was determined using consensus criteria [17]. Comorbidities were defined as previously reported [18]. Recipients of human leukocyte antigen (HLA)-matched related or unrelated transplants were matched at the allele level at HLA-A, -B, -C, -DRB1 and DQB1 (10/10), while haploidentical donors- were mismatched at three or more HLA loci.

Study objectives

The primary study objective was to generate a prognostic score that could predict overall mortality (OM = 1-overall survival) after transplant. The secondary objectives were to predict NRM after alloHCT, confirming the prognostic power of such scores in terms of overall mortality (OM) and NRM at 2 years [19].

Statistical analysis

During the dataset cleaning, to reduce the effect of outliers, an individual was excluded from the study in the following cases: weight <30 kg or >205 kg; height <100 cm or >230 cm; body mass index (BMI) > 70; or donor age <15 or >70 years. In this study, we used only complete cases and excluded individuals with missing values in any of the covariables. Since the AI models used for the analysis did not take into account the time to event, the model was built considering a fixed outcome at 2 years (alive or dead) for OM. Patients who died within 2 years and patients alive or dead at >2 years post-transplant were included in the model; alive patients with a follow-up time of <2 years were excluded. For NRM, a similar score was built but patients who relapsed before 2 years were also included.

Logistic models designed to predict the probability of the patient status by calculating the log-odds for the event by a linear combination of all covariables [20]. Then, a stepwise Akaike information criterion (AIC) method was used to select the most important variables [21]. A support vector machines method (SVM) was carried out testing different kernels (linear and radial) and different cost functions. Best results were obtained with a radial kernel and cost = 10. SVM are supervised learning models (linear or not linear) that map training samples to points in space maximizing the width gap between the two groups. Then, test samples are mapped into the same space and are classified into one of the categories based on which side of the gap fell [22]. A random forest (RF) model was generated by trying different hyperparameters, the best being those with 1000 trees and mtry of 7. RF is an ensemble learning method used in this work for classification. It builds a multitude of decision trees in the training and classifies the test with the class selected by most trees. Extreme Gradient Boosting (XGBoost) was implemented with the following optimized hyperparameters: max_depth = 10, eta = 0.05, nthread = 50, subsample = 0.8, and nrounds = 25. Boosting ins an ensemble learning technique that from several weak classifiers in series builds a strong classifier. Furthermore, XGBoost is an extension to gradient boosted decision trees that were specially designed to improve in terms of performance and speed [23]. Lastly, for elasticnet (EN) we used a tunelength of 25. EN is a regularized regression hybrid method that linearly combines two of the most often used regularized linear regression techniques (Lasso and Rige) that both classifies into groups and select the most important variables at the same time [24]. In all the Machine Learning methods that predict probabilities, the cut-off used to classify the binary data was 0.5.

With respect to neural networks, we built a 4-layer model. Neurons in hidden layers were set in descending order (64, 32, 16, 8). Each layer included batch-normalization to prevent the vanishing gradient problem. After each layer, a dropout of 30% was applied to avoid overfitting. The Swish function was used in each layer as the activation function in order to alleviate gradient problems. The output layer consisted of only one neuron with a sigmoid function due to the binary classification problem. The network was trained with loss function typical for binary classification. Additionally, the "Adam" optimizer was used for network training, with a learning rate of 0.01. Training was performed for 25 epochs with a batch size of 512.

For the OM, data were quite balanced in terms of the percentage of patients alive or dead at the 2-year landmark (43% of deaths were within 2 years so 57% were alive at 2 years). Thus, models were trained with 70% of the study population. Test and validation datasets were each composed of 15% of the study population. For NRM, since the data were not balanced (22% of non-relapse deaths in <2 years and 78% of alive patients, relapse-related deaths or non-relapse deaths that occur at >2 years), we applied the following procedures. First, we subsampled the training set in order to balance the two categories (with the event and without the event, almost 6000 samples in each group). The models were then trained with the balanced dataset. This process was repeated 10 times in order to compose the training dataset with a different population. Finally, in order to evaluate the performance of the models, the mean of the metrics of these 10 models was considered. The test and validation datasets remained unbalanced to reflect proper representation of the population. Point estimation of OM and NRM were given with their 95% confidence intervals (CI). All tests were two sided with a significance level of 0.05. All the calculations were performed using R software version 4.1.2 [25].

Table 1. Baseline characteristics of the study cohort.

Characteristics	Data ($n = 33,927$)	Train ($n = 23,749$)	Test ($n = 5089$)	Validation ($n = 5089$)
Median age at HCT (range)	52 years (18–80 years)	52 years (18–80)	53 years (18–77)	52 years (18–79)
Karnofsky score at HCT ≥ 90% (%)	24,957 (73.6%)	17,505 (73.7%)	3711 (73.0%)	3741 (73.5%)
Solid tumor, previously present (%)	1410 (4.2%)	969 (4.1%)	212 (4.2%)	229 (4.5%)
Inflammatory bowel disease, previously present (%)	220 (0.6%)	154 (0.6%)	31 (0.6%)	35 (0.7%)
Rheumatological comorbidity (%)	341 (1.0%)	240 (1.0%)	56 (1.1%)	45 (0.9%)
Infections present before HCT (%)	1918 (5.7%)	1366 (5.6%)	269 (5.3%)	283 (5.7%)
Diabetes (requiring treatment other than diet alone) (%)	1067 (3.1%)	763 (3.2%)	162 (3.2%)	142 (2.8%)
Renal comorbidity (moderate to severe) (%)	274 (0.8%)	190 (0.8%)	45 (0.9%)	39 (0.8%)
Hepatic comorbidity (%)	943 (2.8%)	659 (2.8%)	119 (2.3%)	165 (3.2%)
Arrhythmia (conduction blocs) (%)	515 (1.5%)	366 (1.5%)	73 (1.4%)	76 (1.5%)
Cardiac comorbidity (%)	1388 (4.1%)	973 (4.1%)	200 (3.9%)	215 (4.2%)
Cerebrovascular disease: stroke/CNS hemorrhage (%)	343 (1.0%)	240 (1.0%)	45 (0.9%)	58 (1.1%)
Heart valve disease (%)	334 (0.9%)	224 (0.9%)	68 (1.3%)	42 (0.8%)
Pulmonary comorbidity (%)	5214 (15.4%)	3649 (15.3%)	758 (14.9%)	807 (15.9%)
Obesity (%)	973 (2.9%)	684 (2.9%)	144 (2.8%)	145 (2.8%)
Peptic ulcer (%)	143 (0.4%)	103 (0.4%)	19 (0.4%)	21 (0.4%)
Psychiatric disturbance (%)	993 (2.9%)	662 (2.6%)	155 (3.0%)	156 (3.1%)
Total comorbidities				
• 0	22,319 (65.8%)	15,656 (65.9%)	3359 (66.0%)	3304 (64.9%)
• 1	1369 (4.0%)	942 (4.0%)	219 (4.3%)	208 (4.1%)
• 2	6263 (18.5%)	4366 (18.4%)	925 (18.2%)	972 (19.1%)
• 3	2801 (8.3%)	1965 (8.3%)	411 (8.1%)	425 (8.4%)
• >3	1175 (3.5%)	820 (3.5%)	175 (3.4%)	180 (3.5%)
CMV antibodies in patient	23,026 (67.9%)	16,125 (67.9%)	3424 (67.3%)	3477 (68.3%)
CMV antibodies in donor (%)	18,766 (55.3%)	13,158 (55.4%)	2784 (54.7%)	2824 (55.5%)
Donor sex female to patient sex male (%)	12,876 (37.9%)	9094 (38.3%)	1889 (37.1%)	1893 (37.2%)
Type of donor (%)				
• Identical sibling	14,921 (43.1%)	10,435 (43.9%)	2262 (44.4%)	2224 (43.7%)
• Matched unrelated donor (> 9/10)	14,629(43.1%)	10,249 (43.1%)	2173 (42.7%)	2198 (43.2%)
• Haploidentical	4386 (12.9%)	3065 (12.9%)	654 (12.8%)	667 (13.1%)
Graft type				
• Bone marrow	4767 (14.1%)	3332 (14.0%)	707 (13.9%)	728 (14.3%)
• Peripheral blood	29,160 (85.9%)	20,417 (86.0%)	4382 (86.1%)	4361 (85.7%)
Conditioning intensity:				
• Myeloablative (%)	17,721 (52.2%)	12,413 (53.2%)	2689 (52.8%)	2619 (51.8%)
• Reduced-intensity (%)	16,206 (47.8%)	11,336 (47.7%)	2400 (47.2%)	2470 (48.5%)
Disease risk index:				
• Low	2676 (7.9%)	1892 (7.9%)	365 (7.2%)	419 (8,2%)
• Int	21,210 (62.5%)	14,765 (62.1%)	3240 (63.7%)	3205 (63.0%)
• High	8543 (25.2%)	6030 (25.4%)	1266 (24.9%)	1247 (24.5%)
• Very high	1498 (4.4%)	1062 (4.5%)	218 (4.3%)	218 (4.3%)
Ex vivo T cell depletion (CD34+selection) (%)	620 (1.8%)	432 (1.8%)	92 (1.8%)	96 (1.9%)
Use of Post-transplant cyclophosphamide for GVHD prophylaxis (%)	4525 (13.3%)	3134 (13.9%)	709 (13.9%)	682 (13.4%)
In vivo T cell depletion:				
• Only ATG (%)	14,280 (42.1%)	10,020 (42.2%)	2,102 (41.3%)	2,158 (42.4%)
• Only alemtuzumab (%)	2903 (8.6%)	2032 (8.5%)	434 (8.6%)	437 (8.6%)
• ATG+alemtuzumab (%)	77 (0.2%)	52 (0.2%)	14 (0.2%)	11 (0.2%)
• No (%)	16,667 (49.1%)	11,645 (49.0%)	2539 (49.9%)	2483 (48.8%)
Disease diagnosis:				
• Acute lymphoid leukemia (%)	5059 (14.9%)	3529 (14.9%)	759 (14.9%)	771 (15.1%)
• Acute myeloid leukemia (%)	17,311 (51.0%)	12,081 (50.1%)	2622 (51.5%)	2608 (51.2%)
• Myelodisplastic síndromes (%)	4221 (12.4%)	2993 (12.6%)	608 (11.9%)	620 (12.1%)
• Hodgkin disease (%)	1464 (4.3%)	1,043 (4.4%)	221 (4.3%)	200 (3.9%)
• Non-Hodgkin lymphomas (%)	3867 (11.4%)	2686 (11.3%)	573 (11.3%)	608 (11.9%)
• Multiple mieloma (%)	2005 (5.9%)	1417 (6.0%)	306 (6.0%)	282 (5.5%)
Disease status at HSCT				
• Active	7331 (21.6%)	5195 (21.9%)	1067 (21.9%)	1069 (21.0%)
• Complete Remission	23,443 (69.1%)	16,339 (68.7%)	3531 (69.4%)	3573 (70.2%)
• Partial Remission	3153 (9.3%)	2215 (9.3%)	491 (9.7%)	447 (8.8%)

CMV cytomegalovirus, *GVHD* Graft-versus-host disease, *HCT* Haematopoietic Cell Transplantation, *JACIE* Joint Accreditation Committee ISCT EBMT.

RESULTS

Patient characteristics

The dataset contained 33,927 patients and was used for the analysis (Table 1). Median follow-up time for survivors was 59.3 months. OM and NRM at 2 years were 42.5% (95% CI = 42.0–43.0%) and 22.6% (95% CI = 22.1–23.1%), respectively (Fig. 1).

Prognostic score building and correlation with survival

The seven models predicted 2-year OM and NRM with similar AUC values (Table 2). The best models were, for OM, gradient boosting (XGBoost) with AUC = 0.64 (95% CI = 0.62–0.65, Fig. 2a) and for NRM, elasticnet with AUC = 0.62 (095% CI = 0.61–0.63). Neural networks had a slightly higher performance for NRM but have limitations regarding the explainability of results. The same results were observed when performing the analysis with the subset of the haploidentical cohort ($n = 4386$): AUC for OM = 0.66 (95% CI: 0.63; 0.69) and AUC for NRM = 0.63 (95%CI 0.63; 0.64). Using the same XGBoost model to calculate OM but restricted to the total number of comorbidities as a surrogate for the HCT-CI (AUC = 0.58, 95% CI = 0.54–0.62, Fig. 2b) and Disease Risk index (AUC = 0.61, 95% CI 0.60–0.63, Fig. 2c), the results were lower than the newer model (but only statistically different between the new score and the total number of comorbidities). For the logistic regression analysis, the final results are reported in Table S1. In the final prognostic score including all the variables, gradient boosting was used to predict OM and elasticnet to predict NRM. The final score gave a continuous risk value (0–100%) for each patient. Patients with the lowest score had a 2-year OM and NRM of 18 and 13%, respectively, while patients with the highest scores had a 2-year OM and NRM of 82 and 93%, respectively. In order to confirm the prognostic capacity of the score, we created a visual representation of the possible prognostic results grouped into four risk classes (Fig. 3a, b).

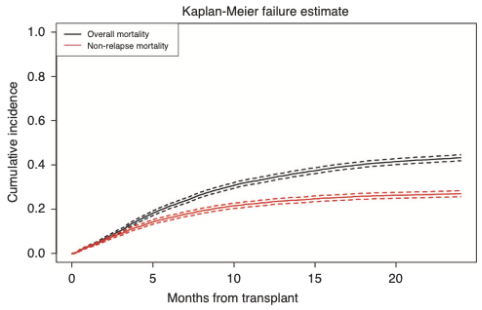

Fig. 1 Overall mortality and non-relapse mortality of the whole cohort. Kaplan–Meier representation of overall mortality (black curve) and non-relapse mortality (red curve) of the overall cohort.

DISCUSSION

Prognostic scores were introduced in the alloHCT setting more than 20 years ago in order to help the clinician to select patients who are suitable for transplantation. The HCT-CI, derived from the Charlson comorbidity index, was the first to be introduced; it has been validated in different studies [8, 26] and has also been shown to be highly reproducible [27]. This score allowed hematologists to perform a specific pre-transplant comorbidity evaluation that could predict OM and NRM at 2 years post alloHCT with sufficient accuracy, and thus they were finally able to stratify patients. Many institutions have also adopted this score to exclude patients from the alloHCT procedure in case of a higher risk of toxicity (score ≥ 3). In recent years, various groups have tried to improve these scores by also considering biomarkers or the patient's age, resulting in a small but significant improvement in the score [10, 28]. When we look at the population from which the study derived, several observations can be made. Patients were from the same hospital, limiting the external validation of the score. The time period was from 1997 to 2003, with a bias towards significantly worse outcomes compared to current alloHCT (CIT). Moreover, the types of alloHCT available today, such as haploidentical donor transplant, as well as PTCy GVHD prophylaxis were excluded or did not exist at that time. In subsequent years, other scores were created in an attempt to improve mortality prediction. The pre-transplant assessment of mortality (PAM) score (2006) and its revised version increased the population size and incorporated patient-, disease- and transplant-related characteristics (patient age, donor type, disease risk, conditioning regimen, FEV1, carbon monoxide diffusing capacity, serum creatinine level, and serum alanine aminotransferase concentration). The EBMT score (2009) increased the statistical power using data from the European registry ($n = 56,050$), and donor as well as disease characteristics were considered (patient age, disease stage, time from diagnosis, donor type, and donor-recipient sex combination). More recently, the Acute Leukemia EBMT score (2015) maintained a large number of patients and considered more variables (disease stage, Karnofsky performance score, donor type, recipient donor CMV serostatus, and HSCT year, while age, diagnosis, days from diagnosis to transplantation, conditioning regimen, and annual number of transplantations were dependent variables) thanks to a machine learning strategy. In summary, none of these scores proved to be significantly better than the others, and most biases present in the original HCT-CI (previous patient cohorts, exclusion

Table 2. Performance of standard and artificial intelligence-based methods in predicting overall mortality and mortality related to toxicity expressed through area under the curve (AUC) values.

AUC	All patients		Haploidentical cohort	
	OM (95% CI)	NRM (95% CI)	OM (95% CI)	NRM (95% CI)
Logistic	0.62 (0.61;0.64)	0.56 (0.57;0.57)	-	-
Support Vector Machines (linear)	0.61 (0.60;0.62)	0.61 (0.60;0.62)	-	-
Support Vector Machines (radial)	0.62 (0.61;0.63)	0.54 (0.53;0.56)	-	-
Random Forest	0.63 (0.62;0.65)	0.55 (0.54;0.56)	-	-
Gradient boosting	0.64 (0.62;0.65)	0.57 (0.56;0.58)	0.66 (0.63;0.69)	-
ElasticNet	0.63 (0.62;0.65)	0.62 (0.61;0.63)	-	0.63 (0.62;0.64)
Neural Network	0.64 (0.63;0.65)	0.61 (0.62;0.63)	0.67 (0.65;0.69)	0.63 (0.61;0.64)

AUC Area Under the Curve, *OM* Overall Mortality, *NRM* Non-Relapse Mortality.

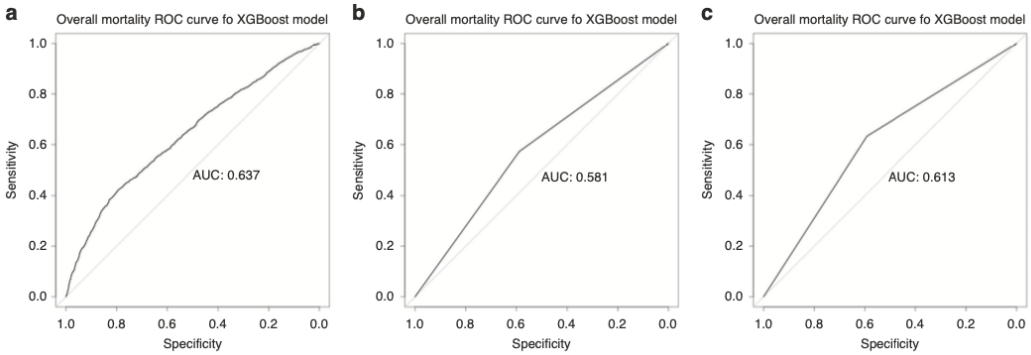

Fig. 2 Receiving operator curve (ROC) for overall mortality. XGBoost model with all the variables (**a**), with total comorbidities only (**b**) and with Disease Risk Index (**c**).

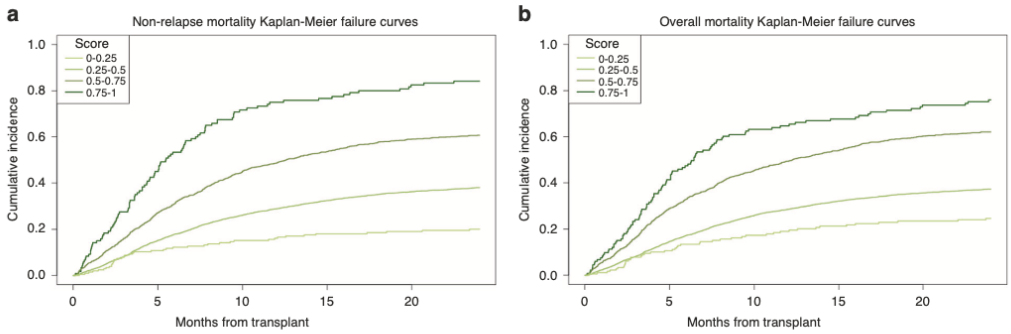

Fig. 3 Overall mortality stratification. Visual representation of the prognostic capacity of the overall mortality (**a**) and non-relapse mortality (**b**) scores calculated, grouping the final probability into four groups: 0–25%, 25–50%, 50–75%, and 75–100%.

of haploidentical and PTCy patients) were not adequately addressed in every score.

In our study, we reported an OM-related AUC which is in line with previous reports. In fact, our AUC of 0.64 compares well with other prognostic AUC scores usually included within the 0.55–0.70 range [29]. Although our study did not show a significant advantage over other scores in terms of accuracy, the following advantages make this score potentially more useful than previous ones. First, considering the improvements in alloHCT made during the last decade in comparison to 2000–2010 [4], we decided to include only alloHCTs performed between 2010 and 2019 in our population. In the other scores, study populations were derived from the mid-1990s or the first decade of the 2000s. Such a time interval is of fundamental importance. In fact, it is only from 2008 that we witnessed an increase in haploidentical alloHCTs thanks to the widespread use of PTCy, which is generally considered the most important innovation in the setting of alloHCT in the last 15 years [30]. Bearing this in mind, we tested the accuracy of our test in the haploidentical cohort ($n = 4386$) and confirmed the acceptable AUC results in this patient subgroup as well (AUC = 0.66). Another advantage of this score lies in the exploitation of a large number of patients from the EBMT registry. Such a large cohort of patients, coupled with the use of AI-derived statistical techniques, allowed us to consider all the most important variables that have a prognostic impact on alloHCT mortality. In fact, we were able to include variables from the three main factors impacting clinical outcomes: patient, transplant type, and disease status. To date, this is the most comprehensive score that can be calculated using pre-transplant factors obtainable from registry data. Of note, the use of PTCy was considered as a specific factor ($n = 4525$) that had never been taken into account before. Considering the significant impact of PTCy on reducing GVHD, it is fundamental to specify whether this strategy is used or not, especially in the haploidentical setting. Only the AL-EBMT score from Shouval et al. has similar characteristics to our score in terms of methodology and comprehensive inclusion of prognostic variables. However, the AL-EBMT score relies on an older cohort of patients and excludes haploidentical and PTCy patients. Moreover, it is applicable only to acute leukemias, while our score can be used for the most common oncohaematological indications: acute leukemias, lymphomas, plasma cell tumors and myelodysplastic syndromes. Finally, our system is able to discriminate the risk category of patients more precisely. Despite not yet being a true personalized score (due to lack of an optimal accuracy level), we are finally able to rely on more exact probabilities of mortality or NRM than previous scores. A common example is the case of patients with a HCT-CI score of ≥3 points. Beyond this cut-off value, many patients will be excluded from transplant procedures in many centres. However, it is not possible to discriminate between patients with a HCT-CI of 3 and patients with higher scores, making it extremely difficult to exclude patients from a lifesaving procedure such as alloHCT. With this newer score, better stratification of high-risk patients is also expected to aid the clinicians in improving their classification.

So far, we recognize that this score is perhaps more comprehensive and modern than previous instruments, but it

requires a large number of variables and time to run the analysis. However, if the transplantation field can enter the AI era this should not be a barrier. In clinical practice, our score could be used only for high-risk patients for whom, based on clinical evaluation and/or classified as high risk with other simpler scores, a more precise estimation of transplant-related toxicity is needed. However, considering that AUC values between 0.60 and 0.70 are considered as moderate in terms of accuracy, we recommend that our score (or any other previous score) should not be used on its own to exclude patients from a lifesaving procedure. The exclusion from alloHCT should always consider a comprehensive view of the patient and his/her disease by the clinicians. Future scores might be improved by incorporating other clinical and biological characteristics. More recent scores evaluating the performance status of a patient in depth, such as geriatric scores, could be implemented in the pre-transplant evaluation [15, 31], and biological biomarkers such as the endothelial damage reflected by the EASIX score could improve the accuracy of the prediction [13, 32]. In the future, big data analysis and AI strategies that incorporate multiple types of clinical and biological data to finally obtain a personalized score in the alloHCT setting will become a reality. A final consideration regarding our study is that the concept of mortality or toxicity risk associated with alloHCT is not a static concept. In fact, in our daily practice, we see how the risk of severe toxicity after alloHCT is a dynamic process that may change depending on the time from transplant and events that follow the procedure, such as infections, toxicity of the conditioning regimen and incidence of GVHD. In this sense, a recent AI-based prognostic score for patients receiving liver transplant has shown an AUC higher than 0.80 in predicting mortality at 1 year from the procedure [33]. This score incorporated both clinical and biological patient features. More interestingly, this score was dynamic and could be modified depending on post-transplant follow-up. Thus, it was possible to predict the risk of having different post-transplant complications according to the time from the procedure with high accuracy. Such a model is a potential example of how, in the future, we should incorporate AI models into our clinical practice and use them to support our decision-making dynamically.

In conclusion, our score was able to predict OM and NRM in the current era, including haploidentical transplants and PTCy GVHD prophylaxis, which were not included in previous scores. However, it was not able to improve prediction capacity despite its robust methodology. This confirms previous observations underlining that the results of a prognostic score alone should not be used to exclude patients from a lifesaving procedure. In such high-risk cases, more comprehensive evaluations (e.g. geriatric scores), biological scores (e.g. EASIX score) and the patient's overall clinical phenotype should be evaluated to aid in this difficult therapeutic decision-making.

DATA AVAILABILITY

The study data belong to the EBMT and may be requested through previous authorization.

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AUTHOR CONTRIBUTIONS

MA, RSB, SA were responsible for the overall research questions and design of the study. RSB, MV, GJE performed the statistical analyses. MA, RSB wrote the original draft. PC, GJE, PE, KN, BD, PLR, KA, MA, SM, HRM, BM, SU, SH, FE, PU, RP, AE, CP, YAI, CC, CF, ST, AM, KC, MI, PO, SH, MM, GB, BG, PZ reviewed and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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DISCUSSION

The development and widespread adoption of PTCy-based GVHD prophylaxis has revolutionized alloHCT. This approach has opened the door to successful transplants using HLA-mismatched donors, specifically haploidentical donors (partially matched from a family donor). This is particularly beneficial for patients who lack a readily available MUD in international registries. (112) While haploidentical donors offer a faster and more readily available option, the question remains: is this the best approach for all patients undergoing alloHCT with PTCy-based GVHD prophylaxis?

Prior research provided limited evidence on the optimal donor source (MUD vs. haploidentical) when using PTCy for GVHD prevention. Our study aims to bridge this knowledge gap in the setting of lymphoproliferative diseases.

We investigated the optimal donor source for patients with non-Hodgkin lymphoma (NHL) and HL undergoing alloHCT with PTCy-based GVHD prophylaxis. Interestingly, even within this PTCy framework, patients receiving transplants from MUDs displayed a significant OS advantage compared to those receiving transplants from haploidentical donors as already known in the context of methotrexate-based GVHD prophylaxis.

This observed benefit can be attributed to two key factors. The first one is a lower NRM. We found a lower rate of NRM in the MUD cohort. This suggests a potentially safer transplant process for patients receiving MUD transplants, likely due to a better immunological match between donor and recipient. The second factor is a reduced GVHD incidence. Compared to the haploidentical donor group, MUD recipients experienced lower rates of both acute and chronic GVHD. This translates to less immune-mediated and infectious complications related possibly to the use of anti-GVHD drugs. These findings align with a recent study by Gooptu et al. (90) Their research on patients with myeloid malignancies undergoing RIC/NMA alloHCT also demonstrated a survival advantage for MUD over haploidentical donors. This benefit was similarly attributed to a higher NRM in the haploidentical cohort, which Gooptu et al. linked to a higher incidence of acute GVHD and possibly higher infection-related deaths (namely fungal infections).

Cohort characteristics are important for interpreting the results. Nearly 70% of patients in both the MUD and haploidentical donor groups received a RIC/NMA regimen, which is a standard approach for lymphoma patients undergoing alloHCT. This focus on RIC/NMA helps explain some key differences between our study and the Gooptu et al. study. Their research involved patients with myeloid malignancies who received more intensive conditioning regimens. This difference in conditioning intensity could contribute to the lower NRM observed in our study.

Another key factor influencing our findings is the type of graft used. The MUD cohort predominantly received PBSC grafts, while the haploidentical donor group more frequently received BM grafts. This distinction is important because PBSC are known to lead to faster platelet recovery after alloHCT. (60,113) This explains the observed shorter platelet engraftment time in the MUD group.

While our study suggests MUD offer a survival advantage with PTCy-based GVHD prophylaxis for NHL, these findings might not be directly comparable to studies involving different patient populations, conditioning regimens, or graft sources.

However, it's important to acknowledge the existence of conflicting data from other studies. One such example is a recent meta-analysis by Gagelmann et al. (114) Their research compared MUD and haploidentical alloHCT for lymphoma patients and found higher relapse rates associated with haploidentical alloHCT despite using PTCy. A critical factor differentiating the current study from Gagelmann's meta-analysis lies in the GVHD prophylaxis employed for the MUD cohort. The current study utilizes PTCy-based prophylaxis, while the MUD cohort in Gagelmann's analysis primarily received ATG-based regimens.

Independently from the survival advantage of MUD over haploidentical alloHCT in our study, a second important observation are the promising results of PTCy as an effective strategy for GVHD prophylaxis in MUD alloHCT for NHL and HL patients. The findings demonstrate comparable transplant outcomes between PTCy-based MUD alloHCT and our previously published results using traditional calcineurin inhibitor based GVHD prophylaxis regimens for

MUD alloHCT. (41) Overall Survival at 2-year for MUD alloHCT with PTCy in our study (72%) is comparable to the 3-year OS rates observed in our previous study with MUD alloHCT using standard calcineurin inhibitors prophylaxis (62% without ATG and 50% with ATG). Relapse Incidence at 2 years was 22% for the PTCy-based GVHD prophylaxis versus 28% and 36% with calcineurin inhibitors without ATG and with ATG. Non-Relapse Mortality at 1 year was 12% for the PTCy population versus 13% and 20% for calcineurin inhibitors. The PFS was 63% at 2 years for PTCy versus 49% and 28% at 3 years for the calcineurin inhibitors population. The cumulative incidence of grade 2-4 acute GVHD at a comparable time point (day +100) suggests a lower rate for PTCy (24%) versus calcineurin inhibitors (40% and 49%). Finally, cumulative incidence of all grades chronic GVHD at 1 year is lower with PTCy (17% versus 51% and 33%). Overall, these findings suggest that PTCy-based MUD alloHCT offers similar survival rates, but less acute and chronic GVHD incidence compared to traditional calcineurin inhibitors-based MUD alloHCT in lymphoma patients.

While this study suggests promising results with PTCy in MUD alloHCT, definitive confirmation of its efficacy requires well-designed prospective randomized trials like the recently concluded PROGRESS III study. (76) This trial randomly assigns patients to either PTCy-based MUD or traditional calcineurin inhibitors-based MUD alloHCT using RIC/NMA conditioning, allowing for a more robust comparison that minimizes bias. By examining long-term outcomes like GRFS, RI/POD, chronic GVHD incidence, and NRM, this trial established the superiority of PTCy as the new standard of care for MRD and MUD patients. Results in terms of survival results of the MUD cohort of our study and the PROGRESS III trial are similar.

Another important consideration is the success of PTCy-based GVHD prophylaxis in expanding the donor pool, particularly for patients from underrepresented ethnicities who might struggle to find a readily available MUD. The study by Shaw et al. demonstrates the safe application of PTCy in HLA-mismatched unrelated donor alloHCT (with BM grafts). (81) This approach offers a promising avenue for increasing donor availability for these patients.

Finally, we found similar infectious complication-related mortality between MUD and haploidentical donor alloHCT. The current study's finding aligns with previous reports suggesting no significant difference in infectious complications between different HLA

mismatches while using PTCy. (115) However, different GVHD prophylaxis regimens can have varying effects on a patient's susceptibility to infections after alloHCT. Such a difference was described in the PROGRESS III trial where a significantly more elevated incidence of grade 2-3 bacterial infections was reported in the PTCy arm compared to the methotrexate arm (40.0% versus 30.4%) without any impact on NRM. Future studies should specifically address the comparative risks of viral reactivations, fungal infections, and other infectious complications associated with PTCy compared to alternative approaches.

Our study included an analysis of outcomes within the subgroup of patients with HL. This analysis revealed no statistically significant differences in outcomes between patients receiving transplants from haploidentical or MUD donors within the HL subset. However, two potential limitations might have influenced this finding. A low number of patients for this subset could potentially mask any true differences in outcomes between donor types within this specific subgroup. A short follow-up for the MUD cohort might not have been long enough to detect certain long-term outcomes, such as chronic GVHD, which can develop later after alloHCT. These limitations suggest that the lack of observed differences between haploidentical and MUD donors in the HL subset should be interpreted with caution. Future studies with larger patient numbers and longer follow-up specifically focused on the HL population might be necessary to draw more definitive conclusions.

We acknowledge that our study, being of retrospective nature, has some limitations. The use of PTCy-based GVHD prophylaxis in MUD alloHCT cohort is a relatively new approach. This translates to a smaller pool of patients who have undergone this specific type of transplant. This limited data set can restrict the study's statistical power to detect subtle differences in outcomes between MUD and haploidentical donor alloHCT. To address this limitation, an international collaborative effort between the CIBMTR and EBMT groups was necessary. These are the two largest alloHCT registries in the world, and by combining their data, the study was able to analyze a significantly larger patient population compared to a single-center study. This increased sample size strengthens the statistical power and allows for more robust comparisons between donor types. A second limitation of the study was a potential donor selection bias. The study design did not control how transplant centers selected donors. Some centers might have prioritized haploidentical donors due to institutional preferences or time

constraints, while others might have only used them as a last resort after failing to find a MUD. This variability in donor selection practices could introduce bias into the observed outcomes. However, conducting a large-scale, prospective randomized trial directly comparing PTCy-based MUD versus haploidentical alloHCT would be logistically challenging. This is because not all patients will have both a readily available MUD and a suitable haploidentical donor available. The HAPLOMUD (EudraCT-No. 2017-002331-41) phase 3 study is answering this question with a prospective and randomized methodology. However, its results will not be available until the beginning of 2025.

Third, we acknowledge a level of heterogeneity in the patient population across various factors like donor registry, GVHD prophylaxis regimens, graft source, conditioning intensity, and donor age. To address this, we employed multivariable statistical analyses that take these factors into account and adjust for their influence on the observed outcomes. This helps to ensure that the findings are not simply due to pre-existing differences between the MUD and haploidentical donor groups. Moreover, we conducted also two independent sensitivity analyses that incorporate propensity scores. These scores statistically account for potential baseline differences between the groups, further strengthening the reliability of the conclusions.

Fourth, different GVHD prophylaxis regimens were used within the MUD cohort. While the classic approach combines PTCy with cyclosporine and mycophenolate mofetil, a slightly higher proportion of MUD recipients received a 2-drug regimen consisting only of PTCy and calcineurin inhibitors. Previous research from the EBMT suggested a potential benefit for a 3-drug PTCy-based regimen in terms of GVHD and relapse-free survival. (79) Interestingly, despite the higher prevalence of the 2-drug regimen in the MUD cohort, they still experienced lower GVHD rates compared to the haploidentical donor group. This suggests that a 2-drug PTCy-based approach might be sufficient for GVHD prophylaxis in MUD alloHCT. This aligns with findings from recent studies by Mehta et al. (116) Moreover, a recent prospective randomized trial involving HLA-identical donors where PTCy alone, without additional drugs, demonstrated similar outcomes to standard CNI-based prophylaxis. (74)

Graft source disparity is another factor to be considered when interpreting results between the two groups. The haploidentical donor cohort received a higher proportion of BM grafts compared to the MUD cohort, which predominantly received PBSC grafts. To address this potential bias, we conducted an additional analysis restricted to the PBSC population. This analysis confirmed that the overall findings held true even when focusing solely on PBSC grafts.

Finally, our study observed a higher median donor age in the haploidentical donor group compared to the MUD cohort. This difference was considered during the multivariate analysis. However, there are conflicting data from other studies regarding the impact of donor age on transplant outcomes. A recent retrospective study by Perales et al. found no significant influence of donor age on survival when comparing MUD with standard GVHD prophylaxis to haploidentical alloHCT with PTCy for acute myeloid leukemia. (117) Another large retrospective analysis reported that donor age did not negatively impact survival with haploidentical alloHCT using PTCy. (118) However, it did show an association with higher rates of acute GVHD and NRM, which was offset by a lower relapse rate.

In conclusion, our findings suggest that MUD transplants with PTCy-based GVHD prophylaxis might be a better option than haploidentical transplants for non-Hodgkin lymphoma patients, assuming a readily available MUD donor. However, this advantage is limited for patients who lack a suitable MUD match, particularly those from non-European Caucasian backgrounds. For these patients, haploidentical transplants using PTCy offer an acceptable alternative treatment approach for this high-risk disease.

After we reported how to improve the survival of patients receving an alloHCT with PTCy based on donor selection, we focused on how to improve outcomes depending on candidate to transplant selection. Thus, a better use of prognostic factors. The introduction of prognostic scoring systems empowered clinicians to make more informed decisions about patient selection for this complex procedure. The HCT-CI emerged as the frontrunner in this arena. Building upon the established Charlson comorbidity index, (119) the HCT-CI specifically addressed the needs of alloHCT patients. (96) Rigorous validation confirmed its effectiveness, and its high reproducibility ensured consistent results across different healthcare settings.

(120) This innovation transformed pre-transplant evaluation. Hematologists could now leverage the HCT-CI to perform a targeted assessment of a patient's underlying health status, considering the presence and severity of various medical conditions (comorbidities). Armed with this objective data, clinicians gained the ability to predict a patient's risk of experiencing two critical post-transplant complications: OM (the chance of death from any cause within two years after alloHCT) and NRM (mortality arising from causes other than the original disease's return). By categorizing patients into distinct risk groups based on their HCT-CI scores, doctors could prioritize those most likely to experience successful outcomes from alloHCT. Recognizing the score's potential, many institutions have integrated the HCT-CI into their alloHCT selection process. This has led to a more nuanced approach, where patients with a high risk of transplant-related complications (typically those scoring 3 or above) might be directed towards alternative treatment options. While the study provides valuable insights, generalizing its findings requires considering the patient population. The single-center design limits the score's applicability to other institutions. Additionally, the study period (1997-2003) doesn't reflect the significant improvements in overall survival rates observed with current alloHCT practices. Furthermore, the score doesn't encompass recent advancements in alloHCT, such as the use of haploidentical donors and PTCy-based GVHD prophylaxis.

Following the introduction of the HCT-CI, researchers strived to develop even more accurate mortality prediction scores for alloHCT patients. The PAM Score (2006) was built upon the HCT-CI by expanding the study population and incorporating a broader range of patient characteristics. (121) It included factors like age, donor type, disease risk, conditioning regimen, and lung function tests. A revised version of the PAM score further improved upon these aspects. (98)

The EBMT Score (2009), leveraging data from a large European registry (over 56,000 patients), boosted statistical power. (100) This score considered both patient and disease characteristics, including factors like age, disease stage, time since diagnosis, donor type, and compatibility between donor and recipient CMV status. The Acute Leukemia EBMT Score (AL-EBMT, 2015) maintained a large patient population but incorporated even more variables using machine learning techniques. (122) It included factors like disease stage, performance status, donor type, CMV compatibility, year of transplant, and various other patient-specific

characteristics. Overall, these advancements reflect a continuous effort to refine mortality prediction in alloHCT by considering an expanding range of patient, disease, and transplant-related factors. However, none of these scores proved to be superior to the others.

Our study yielded an OM-related Area Under the Curve (AUC) that aligns with previously reported scores. (123) The AUC of 0.64 falls within the typical range of 0.55-0.70 observed for other prognostic scores in alloHCT. While our score doesn't demonstrate a statistically significant improvement in accuracy over existing scores, it offers several potential advantages. Recognizing the advancements in alloHCT practices since the 2000s, (91) we specifically included transplants performed between 2010 and 2019. In contrast, prior scoring systems often relied on data from the mid-1990s or early 2000s. This time difference is crucial because the widespread use of PTCy in haploidentical transplants, considered a major innovation in alloHCT over the past 15 years, only began around 2008. (124) To ensure our score's relevance in the contemporary alloHCT landscape, we evaluated its accuracy within the haploidentical transplant cohort (n=4,386). The results were encouraging, with an acceptable AUC of 0.66 in this subgroup. By incorporating data from a more recent timeframe and demonstrating its effectiveness in the setting of haploidentical transplants, our score offers a potentially valuable tool for mortality prediction in modern alloHCT practice.

To create and validate our new score, we exploited two advantages of our era: the use of large registry data and the artificial intelligence methodology. This allowed us to encompass a wider range of variables that significantly influence alloHCT mortality outcomes. We incorporated variables spanning all three critical factors that impact clinical outcomes – patient characteristics, transplant type, and disease status. This comprehensive approach provides a more nuanced picture of patient risk compared to previous scores. Moreover, this score is the first to specifically account for the use of PTCy (n=4,525) as a variable. Given the substantial role PTCy plays in reducing GVHD, especially in haploidentical transplants, including this factor is crucial for accurate risk assessment.

The AL-EBMT score offers a similar approach in terms of methodology and variable inclusion. However, it's important to note that this score relies on a dated patient cohort and doesn't include patients who received haploidentical transplants with PTCy, a critical innovation in

alloHCT. Additionally, its application is limited to acute leukemias, restricting its usefulness. Our score, in contrast, is applicable to a wider range of conditions, encompassing the most common oncohematological indications.

Our system offers a significant advancement in patient risk assessment for alloHCT. While it does not achieve the level of accuracy necessary for a truly personalized score, it provides a substantial improvement over previous method. Traditionally, scores like the HCT-CI rely on a single cut-off point (e.g., HCT-CI ≥ 3). This approach often leads to excluding all patients above the cut-off from potentially lifesaving alloHCT procedures. However, it fails to differentiate between patients within that high-risk category. Our system moves beyond this limitation by offering more precise probabilities of mortality or NRM for individual patients. This allows for a finer-grained risk stratification within the high-risk group. By providing a more nuanced picture of patient risk, our score equips clinicians with valuable information to make more informed decisions. This can help them better classify patients and potentially identify those who might still benefit from alloHCT despite a high HCT-CI score. However, the use of our score could be time consuming due to the elevated number of variables required to be performed. Said that, we are finally entering the artificial intelligence era and working with more data should not be viewed as a problem if the goal is to improve precision and accuracy. In real-world practice, our score is most valuable for high-risk patients identified by clinical assessment or other simpler scoring systems. For these individuals, our score can provide a more refined estimation of transplant-related mortality and NRM risks.

It's important to acknowledge that scores like ours, with AUC values between 0.60 and 0.70, fall into the "moderate accuracy" category. Therefore, we strongly recommend that our score (or any other scoring system) should not be used as the sole basis for excluding patients from alloHCT. Clinicians should always consider the entire clinical picture, encompassing both the patient and their specific disease, when making such critical decisions. Future advancements in scoring systems might be achieved by integrating additional clinical and biological characteristics. The field of pre-transplant evaluation is poised for further refinement by incorporating more comprehensive assessments of patient health. Geriatric Scores delve deeper into a patient's functional status, potentially improving risk stratification. (111,125) Biomarkers-based scores like the EASIX score, which reflects endothelial damage, (99,126)

offer insights into a patient's biological health and could contribute to more accurate predictions.

Looking ahead, the power of big data analysis and artificial intelligence holds immense promise. By integrating various types of clinical and biological data, these advanced techniques could pave the way for truly personalized scores in alloHCT. This would allow for a more precise understanding of individual patient risk, ultimately enabling clinicians to make the most informed decisions about transplant suitability. A crucial consideration for our study, and for transplant risk assessment in general, is the dynamic nature of risk after alloHCT. Unlike a static snapshot, the risk of severe toxicity is constantly evolving. Factors like time since transplant, infections, conditioning regimen side effects, and GVHD all play a role in this evolving risk profile. This highlights the limitations of static scores like ours. A recent AI-powered score for liver transplant recipients achieved an AUC exceeding 0.80 for predicting one-year mortality. (127) This score not only incorporated both clinical and biological data, but it was also dynamically adaptable based on post-transplant follow-up information. This allowed for highly accurate predictions of various post-transplant complications at different time points. Such dynamic AI models represent the future of risk assessment in alloHCT. By integrating data throughout the post-transplant course, these models can continuously update risk profiles and provide more nuanced guidance for clinical decision-making. Our study paves the way for incorporating such advanced methods into routine clinical practice for the benefit of alloHCT patients.

In conclusion, our study successfully developed a score that predicts OM and NRM in the contemporary alloHCT setting, encompassing factors like haploidentical transplants and PTCy-based GVHD prophylaxis, which were absent in older scores. While this methodology demonstrated robustness, the score itself didn't achieve a significant improvement in overall predictive accuracy. This reinforces the notion that prognostic scores, like ours, should not be the sole factor in determining patient eligibility for alloHCT, especially in high-risk cases. For such patients, a comprehensive evaluation including geriatric, biological and dynamic factors is crucial. Our work paves the way for further advancements in risk assessment tools, potentially incorporating dynamic AI models like those emerging in other areas of transplantation.

The recent history of transplant has been always characterized by small improvements which taken together allowed for a progressive amelioration of such procedure. Big steps forward also happened in the alloHCT field, the last of them being the introduction of PTCy and letermovir prophylaxis for CMV. In my personal view, the next big step could be a significant reduction of toxicity with the development and the use of targeted therapy for conditioning regimens with the potential of a significant reduction in alloHCT toxicity.(128) While waiting for the next big steps, our efforts as hematologists should always be to offer to our patients the best conditions available to reduce toxicity. “Primum non nocere” should be our principal aim in the setting of a complex procedure such as alloHCT, characterized by a higher toxicity. While many factors of the transplant procedure are clearly established (conditioning regimens, GVHD prohpylaxis, antinfective prophylaxis and treatment), there are many other factors which are strictly depending on physician view. Within such factors, a better selection of candidates to transplant and of the most suitable donor for them, represents an important strategy to reduce alloHCT mortality. Maximum attention should be given to such factors in our daily clinical practice.

CONCLUSIONS

1. MUD alloHCT showed better OS rates at 2 years compared to haploidentical alloHCT, also when using PTCy. Haploidentical alloHCT had a higher risk of NRM compared to MUD alloHCT.
2. Acute and chronic GVHD incidences were higher in haploidentical alloHCT recipients compared to MUD alloHCT recipients. No significant differences were observed in relapse rates between the two types of transplantation.
3. We developed a newer artificial intelligence-based prognostic score to predict NRM and OM after alloHCT. The study's score showed comparable accuracy to previous scores but incorporated modern techniques and a more comprehensive dataset including haploidentical alloHCT with the use of PTCy.
4. Despite its robust methodology, it didn't significantly outperform existing scores and should not be the sole factor in excluding patients from lifesaving procedures. The study underscores the importance of considering various patient factors when predicting outcomes post-transplantation, highlighting the need for comprehensive evaluations and clinical judgment in decision-making.

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ANNEXES

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