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Stem Cell Transplantation in Acute Myeloid Leukemia

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Abstract

Allogeneic hematopoietic stem cell transplantation represents the only potentially curative therapeutic approach for Acute Myeloid Leukemia. The choice to perform an allogeneic hematopoietic transplant is the result of a decision-making process that considers disease-related factors (AML-risk category and the state of disease at the time of transplant), the type of donor available and his characteristics (HLA compatibility, gender, CMV serostatus) and the individual risk associated with the procedure itself. The choice of the appropriate conditioning regimen depends on the patient's age and comorbidities. While the introduction of reduced intensity regimen and the availability of alternative donors allows more patients to be eligible for transplantation, myeloablative conditioning remains the standard of care for fit patients. Disease relapse is the leading cause of treatment failure and new strategies attempting at reducing the relapse incidence post transplantation are currently being investigated.

Keywords: acute myeloid leukemia, allogeneic stem cell transplantation, treatment-related mortality, donor selection, conditioning regimen

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) represents the only potentially curative therapeutic approach for Acute-Myeloid Leukemias (AML) [1]. This approach is often limited by the patient's transplant-eligibility, which depends on age and comorbidities. Moreover, in patients considered at low risk of relapse, allogeneic transplantation can be offered in case of disease relapse rather than in first complete remission. The high percentage of relapse of leukemia is the leading cause for failure of transplant [2]. The outcome of patients who relapse after transplantation is poor, especially for those who relapse within six months after transplantation for which overall survival at two years is often inferior to 20% [3].

Allogeneic HSCT for AML in first CR is indicated, according to The European Leukemia Network (ELN), when the risk of relapse exceeds 30–40% and the advantage in disease-free survival (DFS) that can derive from it is greater than 10% [4].

The choice to perform an allogeneic hematopoietic transplant is the result of a decision-making process that considers the AML-risk category together with the transplant risk calculated by evaluating both age and comorbidities. In adjunct, the decision-making process comprises the assessment of the disease-status at the moment in which the patient comes to the observation of the transplant-physician.

For patients in complete remission of the disease, also, the status of minimal residual disease must be considered [5] so that the most appropriate conditioning regimen and modulation of immunosuppressive therapy post-transplant can be chosen.

2. Indications to allogeneic transplantation for acute myeloid leukemia

2.1 AML-risk categories

2.1.1 Low risk, intermediate risk AML and the role of minimal residual disease (MRD)

The European Leukemia Network (ELN) has recently redefined the risk categories for AML into three risk-groups: favourable, intermediate and adverse according to karyotype and somatic mutations harboring prognostic significance (**Table 1**) [6]. The EBMT has provided guidance on indications for transplantation based on clinical evidence and current practice which was updated in 2019 [7]. According to EBMT indications for transplant-eligible patients with favorable risk in first complete remission, the autologous stem cell transplantation may be an option instead of repeated consolidation cycles if MRD is negative. Allogeneic HSCT (from HLA-identical sibling or unrelated donor) remains an option in case of MRD positivity. A growing body of evidence indicates that the pre-transplant evaluation of minimal residual disease (MRD) has a prognostic significance [8–10] and it has to be considered for the transplant choice. Pre-transplantation positivity of MRD is associated with worse overall survival, disease free-survival and relapse incidence [10]. For Intermediate-risk patients in 1st CR allogeneic transplant from an HLA identical sibling is considered as “standard” while autologous transplantation and HSCT from unrelated-donor and alternative donor are considered clinical options [7]. Mannis et al. retrospectively analyzed data from 334 consecutive adult AML patients who underwent to autologous transplantation between 1988 and 2013. Among these patients, 133 were classified as intermediate-risk according to karyotype. Median relapse-free survival (RFS) was three years and 45% of patients maintain a complete remission at five years. Fifty-four patients relapsed after auto-SCT and of whom 26 underwent to allo-HSCT. Among allografted patients 35% (9/26) died of NRM, 35% (9/26) died of progressive disease, 12% (3/26) lived relapse-free at a

Risk category	Genetic abnormalities
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv.(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11; Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow; Biallelic mutated CEBPA.
Intermediate	Mutated NPM1 and FLT3-ITDhigh; Wild-type NPM1 without FLT3-ITD or with FLT3-ITDlow (without adverse-risk genetic lesions); t(9;11)(p21.3;q23.3); MLLT3-KMT2A; Cytogenetic abnormalities not classified as favorable or adverse.
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv.(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) 25 or del (5q); 27; 217/abn(17p) Complex karyotype, monosomal karyotype; Wild-type NPM1 and FLT3-ITD high; Mutated RUNX1; Mutated ASXL1; Mutated TP53.

Ref. [6].

Table 1.
ELN Risk stratification by genetics.

follow-up of 3.8 years while the remaining five patients lost at follow-up. The authors conclude that ASCT in 1st CR may cure about 40% of patients affected by intermediate-risk AML. However, the study of Mannis et al. is limited by the absence of mutational testing for FLT3-ITD and NPM1 and CEBPA for the vast majority of patients and the risk stratification is based on cytogenetics only [11]. National Comprehensive Cancer Network (NCCN) guidelines do not recommend ASCT as a treatment option for intermediate-risk AML in 1st CR outside of a clinical trial [12]. The recent GIMEMA AML 1310 study evaluated a risk-oriented treatment in intermediate-risk (IR) patients in 1st CR: the patients underwent to autologous or to allogeneic transplantation according to post-consolidation negative or positive MRD respectively [13]. Overall survival (OS) and disease-free survival (DFS) in intermediate-risk MRD-positive patients who underwent to allo-HSCT were comparable to OS and DFS of favourable-risk (FR) patients that underwent to autologous transplantation (IR-MRD+: OS and DFS 70% and 67% respectively – FR: OS and DFS 74% and 61% respectively). In IR-MRD negative patients who underwent to autologous stem cells transplantation (ASCT) OS and DFS were 79% and 61% respectively [13]. MRD was evaluated by detecting Leukemia-associated phenotype (LAIP) by 8-colour multiparametric flow cytometry and the threshold was 3.5×10^{-4} leukemic cells.

Based on the GIMEMA AML 1310 trial, the transplant choice in transplant-eligible intermediate-risk AML patients in 1st CR should be taken according to post-consolidation MRD. Some difficulties limit the application of MRD in clinical practice: the cut-off levels, the absence of LAIP or genetic mutations evaluable as MRD-markers in a portion of AML-patients, experience of the laboratory, the method used for molecular MRD assessment. As regard to cut off levels, a consensus from the ELN recommends 0.1% as the threshold level for MRD-positivity [14]. Some studies indicate that also MRD levels inferior to 0.1% are consistent with MRD [15, 16], although residual leukemic cells between 0.01% and 0.1% may define a good-prognosis sub-group of patients. Further studies are needed to address the prognostic significance of very low levels of MRD. As regards to the method used for molecular MRD assessment, the ELN consensus recommends real-time quantitative PCR (RQ-PCR) as the standard. RQ-PCR can detect up to 0.1% residual leukemic cells, although further improvements will come from more advanced approaches based on techniques not yet validated such as next-generation sequencing (NGS) and digital-PCR. Validated markers for MRD are *RUNX1-RUNX1T1*, *CBF-B/MYH11*, *PML-RAR α* , *NPM1*-mutation. About 60% of AML-patients lacks a somatic mutation suitable for MRD monitoring and *WT1* is not recommended as a marker for MRD [14]. Mutations interesting *DNMT3A*, *TET2* and *ASXL1* loci may persist in CR without having a defined prognostic significance in terms of increased risk of relapse [17].

2.1.2 High-risk AML

The categories comprising high-risk acute myeloid leukaemias (i.e. AML harboring *FLT3-ITD*, monosomic karyotype or complex karyotype, *abn(17p)*, *5q-* or *del(5)*, *7q-* or *del(7)*, *inv.(3)* or *t(3;3)*, *t(8;9)*, *t(8;22)*, AML harboring mutated *RUNX1*, *ASXL1*, *TP53*, secondary and therapy-related AML) have a poor prognosis in the absence of allogeneic hematopoietic transplantation.

As regard to *FLT3*-mutated-AML, the mitigating effect of *NPM1* mutation on outcome has been established [18, 19]. ELN has distinguished between two categories: AML harboring *NPM1*-mutated and *FLT3-ITD* at high allelic ratio or *FLT3-ITD* at low allelic ratio and wild-type *NPM1* are classified into intermediate-risk AML while AML harboring *FLT3-ITD* at high allelic ratio and wild-type *NPM1* are

classified as high-risk AML [6]. Given the high risk of relapse, a recent position-statement by the EBMT recommends allo-HSCT for *FLT3*-mutated AML (also with *NPM1*-mutation) in 1st CR from related or alternative donors. The expert panel also recommends a maintenance treatment with *FLT3*-inhibitor: Sorafenib is the suggested option if the patient is treated outside of a clinical trial [19, 20].

As regards the high-risk categories harboring a particular adverse prognosis AML expressing del(5)/5q-, del(7)/7q-, abn(17p), monosomic karyotype, the EBMT have conducted a retrospective analysis on transplant outcome reporting two-year overall survival and leukaemia-free survival between 27% and 34% and between 20% and 24% respectively [21–23]. The worse outcome was observed in patients expressing both 5q- and abn(17p) [23].

2.1.3 Secondary- and therapy-related AML

Secondary AML (sAML) and therapy-related AML comprise a group of heterogeneous disease that, respect to de novo AML, occur more frequently in elderly patients, most often are chemo-resistant to cytotoxic chemotherapy and have a worse prognosis [24]. Sengsayadeth et al. have conducted a retrospective analysis on 3960 patients affected by sAML undergoing to allo-HSCT between 2000 and 2016. The two years overall survival and disease-free survival were respectively 45% and 39%. The subgroup of patients receiving HSCT not in complete remission experienced the worse outcome (2 years OS and DFS, respectively 35 and 29%) [25]. Recently the Acute Leukemia Working Party of the EBMT published a retrospective registry-based study comparing the outcome of allo-HSCT for sAML and de novo AML patients transplanted in the time interval 2000–2016. The three years overall survival, disease-free survival and cumulative incidence of relapse (CIR) were respectively 60%, 55%, 28% and 46%, 41% and 35% respectively for de novo AML and sAML. In multivariate analysis, sAML was associated with worse OS, DFS and CIR than de novo AML [26]. In patients fit for transplant affected by sAML allo-HSCT must be offered upfront, preferably in 1st CR. Novel agent CPX351 (liposomal formulation of Cytarabine and Daunorubicine in a 5:1 ratio) has been recently approved as induction treatment for these patients and has demonstrated superiority compared to the conventional “7 + 3” schedule [27].

2.1.4 Chemotherapy-refractory AML

The prognosis of patients who fail to reach complete remission after induction chemotherapy is poor. In these patients, five years survival is <10%. Allogeneic transplantation may improve survival to 25–30% [28].

Jabbour et al. compared outcomes of 28 AML primary-induction failure (PIF) patients who underwent to allo-HSCT to that of 149 PIF patients who were treated with salvage chemotherapy alone: results were dramatically in favour of allo-HSCT with a three years OS rate of 39% for allo-grafted patients versus 2% for chemotherapy-only patients [29].

Ferguson et al. in a retrospective analysis on 8907 patients have found that patients who fail to achieve a reduction of myeloid blasts <50% with >15% residual blasts after one course of induction chemotherapy as well as patients who fail to achieve complete remission after two courses of induction chemotherapy have a very dismal prognosis if treated with further chemotherapy. Allogeneic stem cell transplantation may improve survival of these patients [28].

The FLAMSA regimen has been designed for patients with active disease who undergo allo-HSCT. It comprises an initial debulk with Aracytin, Fludarabine and Amsacrine followed by a reduced-intensity conditioning and HSCT [30, 31].

In summary, allogeneic HSCT may rescue about 30% of patients with primary induction or re-induction failure and the improvements in recent years in HLA-typing, donor availability (i.e. haploidentical donors), conditioning regimen and supportive care expand the possibility to give allogeneic transplantation to this category of patients [32]. In primary refractory disease performing more than two induction courses before allogeneic transplantation has no benefit [28, 30]. Duval et al. developed a prognostic score for the outcome of allo-HSCT performed for AML refractory to chemotherapy (named Duval Score). They analyzed data from 1673 patients from CIBMTR registry and developed a score based on five variables: phase of disease at HSCT (PIF or refractory relapse after CR > 6 months versus refractory relapse after CR < 6 months), cytogenetic class of risk (good/intermediate vs. high), circulating blasts (absent vs. present), HLA match (HLA matched related vs. matched unrelated vs. mismatched unrelated vs. haploidentical) and Karnofsky Score (KS: > 90 vs. < 90). Four class of risk correlated with different survival were identified. Three-years OS varied from 40% for score 0 versus 6% for score ≥ 3 [33].

2.1.5 Transplantation in 2nd CR

The current indications for allo-HSCT in 2nd CR include transplantation-eligible patients affected by low-risk AML relapsed after previous chemotherapy or autologous transplantation [7]. Allo-HSCT in 2nd CR may also be offered to patients for whom this procedure was previously considered not indicated or too risky (for example intermediate-risk AML for whom MRD was absent after consolidation chemotherapy, or patients lacking HLA-identical sibling donors and considered unfit for an alternative donor at the time of 1st CR).

Some retrospective analysis by ALWP of EBMT has addressed the role of allogeneic transplantation in 2nd CR of AML. Christopheit and coll. have analyzed 537 patients who have undergone allograft in 2nd CR or first relapse after ASCT: 3-years overall survival (OS), leukaemia-free survival (LFS) and non-relapse mortality (NRM) were respectively 39.5%, 31.5% and 33%. Cumulative incidence of relapse (CIR) was 34.6%. A longer survival correlated with allo-HSCT performed in complete remission than in chemo-refractory relapse, with favorable-risk cytogenetics and with a longer duration of 1st CR (more than ten months in median). NRM was higher in patients undergoing to allo-HSCT from alternative donors than HLA-identical sibling and in those who received Total-body Irradiation (TBI) as part of the conditioning pre-ASCT [34].

Gilleece and coll. published a registry report by the EBMT on allo-HSCT in 2nd CR of AML including 1879 patients transplanted between 2007 and 2016. The global outcome at 2 years were: LFS: 52%, OS: 58%, Relapse Incidence: 30%. NRM was 20%. The results were split by age < 50 or ≥ 50 years old and by the intensity of conditioning. OS and LFS for <50 yrs. old were 61% and 54% respectively (without differences due to conditioning regimen). For ≥ 50 years old OS was respectively 58% and 54% for myeloablative (MAC) and reduced-intensity conditioning (RIC) and LFS was 50% for both conditioning regimens. In multivariate analysis, the intensity of the conditioning regimen did have an impact on NRM that was lower for RIC in patients aged ≥ 50 years (HR 0.54, $p < 0.001$). Overall Survival, LFS, CIR and Graft-relapse free survival (GRFS) were better in patients with longer intervals from diagnosis to allo-HSCT. Performance status (PS) and the cytogenetic class of risk at diagnosis (good, intermediate and adverse) also correlated with outcome [35].

Halaburda K et al. retrospectively analyzed 631 patients affected by Core-binding factor (CBF) AML who were allo-grafted in 2nd CR and reported to the EBMT registry between 2000 and 2014. Five-years OS and LFS were respectively 58% and 54% while relapse and NRM at were 22.5% and 23%. The composite

end-point of Graft-relapse free survival (GRFS) at 2 and 5 years was 40 and 34% respectively. In multivariate analysis, GRFS was associated with three or more additional cytogenetic abnormalities and in vivo T-cell depletion (HR 1.6, $P = 0.03$). A trend for a better GRFS was associated with a transplant from a CMV-seronegative donor and for MRD –negative status at allo-HSCT [36].

Passweg and coll. conducted a retrospective study to compare the impact of a previous ASCT versus chemotherapy consolidation without ASCT on the outcome of allo-HSCT performed in 2nd CR. The study included 2619 allo-grafted patients in 2nd CR between 2000 and 2017. Of these, 417 were previously treated in 1st CR with ASCT and 2202 with chemotherapy consolidation respectively. The patients were not evenly distributed among the two cohorts because patients treated with ASCT respect to those treated with chemotherapy consolidation were younger, had undergone transplantation earlier, had more often an unfavorable karyotype, more often received allo-HSCT from alternative donors than from HLA matched siblings and more often received a RIC than a MAC regimen. Two-years OS, LFS, GRFS and NRM were respectively 58, 50, and 21% for chemotherapy consolidations and 55, 46, 35 and 25% for ASCT-patients. In multivariate analysis risk of NRM, LFS and GRFS were higher for previous ASCT-patients than for previous chemotherapy consolidation patients. As well as in the study of Christopeit NRM of the allogeneic transplant was higher for patients in whom TBI was included in the pre-ASCT conditioning [37]. However, after first relapse, the attempt of a second complete remission is not always successful and if outcome is measured from the time-point of relapse, the overall results are very poor. Infact, only 10% of all AML patients that relapse and are treated with re-induction chemotherapy and subsequently with allogeneic hematopoietic transplantation are survivors at 5 years [38].

In summary, about 50% of patients in 2nd CR of AML, if eligible to transplantation, may be rescued by allo-graft, particularly when 1st CR has been longer than six months [33]. The chance to achieve a second remission after a first relapse is, however, limited. Furthermore, prior autologous transplantation is associated with an increased risk of NRM post allogeneic transplantation and this must be considered when choosing auto-transplantation in 1st CR, in particular for low and intermediate-risk AML.

3. Risk assessment

Allogeneic Hematopoietic Stem Cell Transplantation remains a procedure associated with significant mortality and morbidity.

Once the bone marrow transplant has been established as a therapeutic indication, the candidate has to be evaluated in order to define eligibility for treatment and to choose the most appropriate conditioning regimen.

The study of the factors related to the disease, to the donor characteristics and to the patient's general health allows us to evaluate the probability of post-HSCT non-relapse mortality (NRM).

Here we describe the predictive models used in the clinical practice that quantify the post-HSCT risk profile by integrating all these different factors and therefore predict tolerability to allogeneic BM transplant.

3.1 Disease risk index (DRI)

The score arises from the evidence that the outcome of HCT depends on the state of the disease at the time of transplantation. Armand et al. led to the

development of the Disease Risk Index, conducting a retrospective study involving 1539 patients analyzing information about the disease and its status [39].

It does not take into account factors like age and comorbidities. It categorizes patients into four risk groups with different OS and PFS based on differences in the relapse risk as described in **Tables 2** and **3**.

3.2 HSCT-Comorbidity Index (HCT-CI)

Sorrer et al., through a retrospective analysis study, developed the Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (**Table 4**) [40]. Initially developed in 2005, as an adaptation of the Charlson Comorbidity Index to HSCT, it was revised in 2014 to include the age variable [41]. Compared to the previous scores, the HCT-CI places much emphasis on the patient's general health and organ dysfunctions, analyzing 17 comorbidities as described in **Table 2**. It defines 3 risk groups: score 0 (low risk), score 1–2 (intermediate risk), ≥ 3 (high risk). HSCT-CI was subsequently validated in an independent cohort of patients by Raimondi et al. in 2012 [42]. It is an independent predictor of both NRM and OS. 2 years NRM is 14.7%, 21.3%, and 27.3% in patients having ad HSCT score of 0, 1–2 and > 3 respectively and OS was 56.4%, 21.3% and 41.3% respectively. Patients with low scores should be enrolled in randomized clinical trials or undergoing high intensity conditioning regimens (total busulfan dose > 8 mg / kg, or cyclophosphamide dose > 120 mg / kg or > 60 mg/kg in combination with other drugs, or melphalan dose > 140 mg/mq or total body irradiation dose > 6 Gy), while patients with a high score should be candidates for the reduced intensity/non myeloablative conditioning regimens.

3.3 EBMT score

Another score widely used in transplantation practice is the EBMT risk score [43]. It was introduced more than ten years ago initially for patients with chronic myeloid leukaemia (CML), the most frequent indication for allogeneic stem cell transplantation in those years, and subsequently extended to other haematological diseases. Each of the five factors taken into consideration has the same “weight” and importance on the global risk: age, stage of the disease, time from diagnosis, donor type and donor-recipient gender. The score allows us to predict approximately the 5-year probability of OS and TRM for any disease. The novelty, compared to the HSCT-CI, is the introduction of the concept of the disease stage to improve the score predictivity.

1. By age, 3 categories are identified: < 20 years (0 score points), 20–40 years (1 score point) and > 40 years (2 score points). The introduction of low-intensity conditioning regimes has opened access to allogeneic transplantation also to elderly patients, but this does not take away the fact that mortality is higher in this category of patients.
2. For disease stage, three categories are defined: early disease stage (0 score point) represented by acute leukaemia in first CR, intermediate disease stage (1 score point) in which acute leukaemia in second CR and late-stage disease (2 score points) are included with advanced leukaemia.
3. The time interval from diagnosis to transplant provides a cut-off of 12 months. If the elapsed time is < 12 months 0 score points if > 12 months one score point. For acute leukaemias in the first CR we arbitrarily set as 0.

Disease	Disease risk	
AML favorable cytogenetics	Low	
CLL		
CML		
Indolent B-cell NHL		
ALL	Intermediate	
AML intermediate cytogenetics		
MDS intermediate cytogenetics		
Myeloproliferative neoplasms		
Multiple Myeloma		
Hodgkin lymphoma		
DLBCL/Transformed indolent B-NHL		
Mantle cell lymphoma		
T-cell lymphoma, nodal		
AML adverse cytogenetics	High	
MDS adverse cytogenetics		
T-cell lymphoma, extranodal		
Stage	Stage risk	
1st Complete Remission	Low	
2nd or subsequent CR		
1st PR		
Untreated		
Chronic Phase CML		
2nd or subsequent PR (if RIC)		
2nd or subsequent PR (if MAC)	High	
Induction Failure		
Active Relapse		
Accelerated or Blast Phase CML		
Overall assignment		
Disease risk	Stage risk	DRI assignment
Low	Low	Low
Low	High	Intermediate
Intermediate	Low	
Intermediate	High	High
High	Low	
High	High	Very high
DLBCL, diffuse large B cell lymphoma; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; other abbreviations are as in Table 1 . Ref. [39].		

Table 2.
Summary of disease and stage risk groups from original DRI.

Disease	Stage	No. of patients	HR [†]	Original DRI	Percentage of patients	New DRI Group	2-y OS (%)	95% CI
Hodgkin lymphoma CR		126	0.36	Int	14	Low	66	63–68
CLL CR		81	0.47	Low		Low		
Mantle cell lymphoma CR		160	0.51	Int		Low		
Indolent NHL CR		183	0.53	Low		Low		
AML favorable cytogenetics CR		190	0.64	Low		Low		
Indolent NHL PR		276	0.71	Low		Low		
CLL PR		400	0.78	Low		Low		
CML chronic phase 1/2		390	0.82	Low		Low		
CML advanced phase		69	0.92	Int	63	Int	51	50–52
Mantle cell lymphoma PR		149	0.95	Int		Int		
Myeloproliferative neoplasm	Any	426	0.98	Int		Int		
AML intermediate cytogenetics CR		3611	Ref	Int		Int		
ALL CR1		1023	1.00	Int		Int		
T-cell NHL CR		171	1.00	Int		Int		
Multiple myeloma CR/ VGPR/PR		339	1.03	Int		Int		
Aggressive NHL CR		181	1.05	Int		Int		
Low-risk MDS adverse cytogenetics	Early [†]	103	1.06	High		Int		
T-cell NHL PR		164	1.06	Int		Int		
Low-risk MDS Intermediate cytogenetics	Early [†]	516	1.09	Int		Int		
HL PR		225	1.09	Int		Int		
Low-risk MDS intermediate cytogenetics	Advanced [†]	235	1.18	Int		Int		
Indolent NHL	Advanced [†]	128	1.21	Int		Int		
CLL	Advanced	265	1.22	Int		Int		
High-risk MDS intermediate cytogenetics	Early	364	1.24	Int		Int		
Aggressive NHL PR		205	1.26	Int		Int		
T-cell NHL	Advanced [†]	93	1.41	High	20	High	33	31–35
AML favorable cytogenetics	Advanced [†]	34	1.42	Int		High		
HL	Advanced [†]	85	1.48	High		High		

Disease	Stage	No. of patients	HR [*]	Original DRI	Percentage of patients	New DRI Group	2-y OS (%)	95% CI
High-risk MDS intermediate cytogenetics	Advanced [†]	179	1.56	Int		High		
High-risk MDS adverse cytogenetics	Early	80	1.58	High		High		
ALL CR2		407	1.58	Int		High		
AML adverse cytogenetics CR		175	1.59	High		High		
Mantle cell lymphoma	Advanced [†]	46	1.59	High		High		
High-risk MDS adverse cytogenetics	Advanced [†]	30	1.59	Very high		High		
BL [‡] CR		23	1.65	NA		High		
Multiple myeloma	Advanced [†]	150	1.65	High		High		
ALL CR3		61	1.70	Int		High		
Low-risk MDS adverse cytogenetics	Advanced [†]	32	1.86	Very high		High		
AML Intermediate cytogenetics	Advanced	1227	1.89	High		High		
CML blast phase		52	2.02	Int	4	Very high	23	20–27
ALL	Advanced [†]	235	2.23	High		Very high		
Aggressive NHL	Advanced [†]	154	2.54	High		Very high		
AML adverse cytogenetics	Advanced [†]	76	2.83	Very High		Very high		
BL [‡] PR	Advanced [†]	12	5.21	NA		Very high		

Int, intermediate. Ref. [39].
^{*}Hazard ratio for mortality compared with AML intermediate cytogenetics in CR1.
[†]Advanced stage refers to induction failure or active relapse, including stable or progressive disease for NHL, HL, and CLL.
[‡]Those categories were not included in the original DRI.

Table 3.
Refinement of DRI.

4. Concerning the type of donor, the identical sibling donors will have a 0 point score, while the unrelated ones will have one score point. It is interesting to note how the impact of donor typer is different for different pathologies, having a significant impact on aplastic anaemia and the least of all for acute lymphoblastic leukaemia.
5. Last but not least, the gender difference between recipient and donor. Female donor for male recipient (1 score point) as it has been noted that it leads to a higher NRM, due to increased incidence of acute and chronic GVHD.

Also donor or recipient cytomegalovirus (CMV) seropositivity has a prognostic impact: recently a study showed that, compared to CMV-seronegative recipients who

<i>Comorbidity</i>	<i>HCT-CI score</i>	<i>N</i>	<i>%</i>
Arrhythmia	1	7	3
Cardiac	1	18	9
Inflammatory bowel disease	1	1	0.5
Diabetes	1	5	2
Cerebrovascular disease	1	1	0.5
Psychiatric disturbance	1	10	5
Hepatic-mild	1	10	5
Obesity	1	14	7
Infection	1	28	14
Rheumatologic	2	2	1
Peptic ulcer	2	2	1
Moderate/severe renal	2	8	4
Moderate pulmonary	2	30	15
Prior solid malignancy	3	12	6
Heart valve disease	3	4	2
Severe pulmonary	3	49	24
Moderate/severe hepatic	3	2	1
No comorbidities	0	65	32

Abbreviation: HCT-CI, hematopoietic cell transplantation comorbidity index; N, number of patients. Ref. [40].

Table 4.
Definitions of comorbidities included in the HCT-CI score.

underwent allograft from a CMV-seronegative donor, cases of CMV seropositivity of the donor and/or the recipient showed a significantly decreased 2-year leukemia-free survival (44% vs. 49%, $P < .001$) and overall survival (50% vs. 56%, $P < .001$), and increased nonrelapse mortality (23% vs. 20%, $P < .001$) [44]. In a CIBMTR analysis early CMV-reactivation was associated with lower overall survival (HR: 1.27) and it was confirmed as a poor risk factor for post-transplant outcome [45].

Also cytokine’s encoding gene polymorphisms seem to have a prognostic impact. It has been shown that single nucleotide polymorphisms (SNPs) in the IL-6 encoding gene influence outcome after allogeneic stem cell transplantation as described by Tvedt et al. [46].

4. Donor selection

The selection of a donor is a critical element contributing to the success of hematopoietic cell transplantation (HCT).

Among the many factors that influence the outcome of hematopoietic stem cell transplantation, polymorphism of the classical human leukocyte antigen represents the most important barrier [47]. The human Major Histocompatibility Antigens is located on the short arm of chromosome 6. The MHC falls into three main regions, class I, II and III. The most relevant genes for transplantation belong to class I (*HLA-A*, *HLA-B* and *HLA-C*) and class II (*HLA-DR*, *HLA-DQ* and *HLA-DP*). MCH genes are inherited in a co-dominant manner following Mendelian rules. Therefore,

the probability for siblings to be HLA-identical is 25% [48]. HLA compatibility with the donor is usually defined by high-resolution typing (four digits) for ten alleles, *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DR* and *HLA-DQ*, but there is increasing evidence supporting the relevance of *DPB1* matching [49]. An HLA-identical sibling donor is generally considered the best donor for allo-HSCT; however, less than a third of patients will have one available. For the remaining 70% of patients, alternative sources of stem cells are a matched unrelated adult volunteer donor, a haploidentical donor or a cord blood unit. The probability of identifying a highly matched unrelated donor depends on the frequency of the patient's HLA haplotypes and ethnic origin. 1–5% of patients do not have a single potentially matched donor upon direct interrogation of the BMDW database because the large majority of donors registered in the database are of Western European ancestry. In European countries, 45–65% of patients will eventually have a 10/10 matched donor, and a 9/10 matched donor may be identified for an additional 20–30% of patients [50]. There is a consensus that single *HLA-A*, *B* or *C* allele mismatches and double *HLA-DRB1* mismatches are associated with increased mortality in non-T-cell-depleted bone marrow transplantation [51]. Disparities in *HLA-DQB1*, as well as C-allele disparities in C 03:03 vs. 03:04, have been reported to be permissive with no adverse effects on the outcome [52]. Disparities in *HLA-DPB1* are observed in the majority of *HLA-A*, *HLA-B*, *HLA-C* and *HLA-DQB1* (10/10) MUD transplants [53]. Different studies have demonstrated that biological models can be used to identify selected, permissive *DPB1* mismatches combination, associated with lower clinical risks compared to their high risk, non-permissive, counterparts. There are five different biological models for the assignment of *DPB1* permissiveness that have been identified to date, three of which are based on functional T-cell epitopes (TCE) [54]. A study shows that survival probabilities can be significantly increased by selecting donors with TCE4- permissive *HLA-DPB1* disparities, with a significant association with NRM and OS in 10/10 and 9/10 matched transplantation. Therefore, the UD searches should be directed up-front toward the identification of a 10/10 or 9/10 matched donor presenting TCE4-permissive *HLA-DPB1* disparities [55].

Whenever two or more 10/10 matched donors are available, other factors are studied. We have to evaluate the presence of HLA-antibodies in the recipient and select a donor for whom there are no recipient donor-specific anti HLA antibodies (DSA). An essential element is the donor age with priority for the youngest. Another factor is the matching for patient/recipient CMV serostatus with the best scenario be a seronegative patient receiving from a seronegative donor. Donor gender is also considered with priority for the male donor since female donor can immunize post-pregnancy. Another factor to be considered is ABO-matching, even though the impact of blood group compatibility on outcome has been reported to be modest [56]. Other factors to be considered include NK cell alloreactivity and KIR haplotype matching and non-inherited maternal HLA antigens (NIMA) mismatching [57].

Many advances in MUD HCT have occurred over the past 20 years and several studies suggest that transplantation from fully Matched Unrelated Donor (8/8 or 10/10) and Matched Sibling Donor results in similar survival times for patients with AML [58]. The study of Center for International Blood and Marrow Transplant Research analyzed outcomes of 2223 adult acute myelogenous leukaemia patients who underwent allogeneic HCT between 2002 and 2006 (HLA-Matched related donor MRD, n = 624; 8/8 HLA locus matched MUD, n = 1193; 7/8 MUD, n = 406). The 100-day cumulative incidence of GVHD was significantly lower in MRD HCT recipients than in 8/8 MUD and 7/8 MUD HCT recipients (33%, 51% and 53% respectively; $P < .001$). In multivariate analysis, 8/8 MUD HCT recipients had a similar survival rate compared with MRD HCT recipients. 7/8 MUD HCT recipients had higher early mortality than MRD HCT recipients, but beyond six months after

HCT, their survival rates were similar [58]. Another study compared the outcomes of the unrelated donor (URD, n = 385) with human leukocyte antigen (HLA)-matched sibling donor (MSD, n = 226) transplantation in patients with acute myeloid leukaemia in first complete remission (CR1) having unfavourable cytogenetics at diagnosis. Three-year leukaemia-free survival (LFS) for MSD was 42% compared with 34% for HLA-well-matched URD and 29% for partially matched URD. In multivariate analysis, HLA-well-matched URD and MSD yielded similar LFS and OS. LFS and OS were significantly inferior for HLA-partially matched URD recipients, those with prior myelodysplastic syndrome, and those older than 50 years. Patients with chronic GVHD had a significantly lower risk of relapse [59].

If 10/10 matched unrelated donor is not available, an alternative donor has to be considered: HLA 9/10 matched unrelated donor; haploidentical donor; HLA mismatched unrelated donor; cord blood unit.

A haploidentical related donor is defined by the sharing of one haplotype (or a single identical copy of chromosome 6) with the patient containing the HLA region involving class I and class II histocompatibility genes (patient's parents or sons; sometimes brothers or sisters or cousins). A significant advantage of haploidentical transplantation is the rapid access to a donor which is of crucial importance for patients with high-risk AML since a delay in transplantation due to the donor issues can result in a poor outcome. Today primary prevention and treatment of GVHD have been a major challenge in this peculiar HLA-mismatched setting [60]. Two main platforms have been developed: ex vivo T cell depletion, which is used in a few centers because it is expensive and it needs highly specialized laboratories [61, 62], and unmanipulated graft transplantation, which is way more used since the introduction of Post-transplant Cyclophosphamide (PT-CY) (that will be discussed in the chapter on conditioning regimens). Several studies found that the OS secondary outcomes of patients with AML who received haplo-HSCT were not significantly different from MSD-HSCT and MUD-HSCT [63].

Another alternative source of stem cells is the cord blood unit (UCB). It has been established that a single UCB unit contains sufficient numbers of HSCs for durable engraftment in most patients.

Thanks to immunological immaturity, an advantage of UCB is its apparent reduced alloreactive response as compared with bone marrow. The data would suggest that UCB, despite HLA mismatching, is associated with low GVHD risk. Disadvantages of Umbilical Cord Blood Transplantation are slower engraftment, higher risk of non-immunological rejection (graft failure), remote possibility of transmission of a genetic disease, more significant delay in immune reconstitution, no possibility of donor lymphocyte infusion [64, 65].

A retrospective analysis including 106,188 adult patients with haematological malignancies who underwent allogeneic hematopoietic stem cell transplantation studied overall survival at three years. The results showed: 54.6% for a matched sibling, 51.6% for a matched unrelated donor, 41.3% for a mismatched unrelated donor, 44.2% for haploidentical and 43.7% for cord blood [66]. OS following HSCT is improving with substantial progress among recipients of haploidentical and cord blood HSCT, but the traditional donor hierarchy of matched sibling donors followed by matched unrelated donors and then other donors hold [66].

5. Conditioning regimens

Conditioning is the treatment used to prepare patients undergoing hematopoietic bone marrow transplantation. The role of conditioning is to eradicate the residual haematological disease from the bone marrow, to provide room in the host

bone marrow for the donor stem cells and to have an immunosuppressive effect in order to ensure engraftment.

Conditioning regimens can include Total Body Irradiation (TBI) or they can be radiation-free and be based only on chemotherapy. They usually consist of a myeloablative compound (such as Busulfan or Melphalan) and an immunosuppressive agent (such as Fludarabine or Cyclophosphamide).

Conditioning regimens have been classified into three categories based on the duration of the induced pancytopenia and the requirement for stem cells support [67]:

Myeloablative conditioning (MAC): *a combination of agents expected to produce irreversible pancytopenia; stem cells support is required to rescue marrow function;*

Non-myeloablative conditioning (NMA): *a regimen that will cause minimal cytopenia and does not require stem cells support;*

Reduced-intensity conditioning (RIC): *a regimen that cannot be classified as NMA or MA; it can cause pancytopenia which may be prolonged and do require stem cells support; cytopenia may not be irreversible; RIC regimens differ from MA conditioning because of the dose that must be reduced by at least 30%.*

Traditionally, the two most important myeloablative regimens were TBI/Cyclophosphamide (Cy) (TBI 12 Gy, Cy 60 mg/kg \times 2 days) and BU (Busulfan)/Cy (BU 4 mg/kg \times 4 days and CY 60 mg/kg \times 2 days). In AML, different studies showed the equivalence between these regimens in terms of Leukemia Free Survival (LFS) and Overall Survival (OS) [68, 69]. Cyclophosphamide is often replaced by Fludarabine, a purine analogue with antineoplastic and immunosuppressive effect and a better toxicity profile. The combination BU-FLU (BU 4 mg/kg \times 4 days and FLU 40 mg/m²/day for four consecutive days) has been demonstrated to be as effective as the regimen BU-CY but with a lower Transplant Related Mortality (TRM) [70, 71]. Thiotepa (TT), an alkylating compound with antineoplastic and myeloablative activity, can be added to these combinations in order to reduce the risk of relapse [72].

In the last two decades, the introduction of RIC regimens has revolutionized the transplant landscape by allowing more patients to be eligible for transplantation. RIC transplantation relies more on the graft versus leukaemia (GvL) effect than a cytotoxic action for efficacy. RIC regimens are a good treatment option in older patients (age > 60 years) or younger patients with comorbidities that are ineligible for a MAC regimen [73]. These regimens usually combine Fludarabine with an alkylating agent (like Busulfan or Thiotepa) or TBI in reduced doses. Many studies in the literature comparing MAC and RIC regimens in AML showed a comparable survival; even though a higher relapse rate was observed in RIC regimen, it was balanced by a lower TRM [74–78]. To address this question, a phase III randomized trial comparing MAC with RIC in patients with acute myeloid leukaemia or myelodysplastic syndromes was performed. In this study, RIC resulted in lower TRM but higher relapse rates compared with MAC, with a statistically significant advantage in LFS with MAC. These data support the use of MAC as the standard of care for fit patients with acute myeloid leukaemia [79].

Intermediate-intensity conditioning has been developed to reduce the relapse incidence (RI) while maintaining a reduced TRM after RIC transplantation. The FLAMSA regimen has been designed for patients with active disease who undergo allo-HSCT. It comprises an initial debulk with Aracytin, Fludarabine and Amsacrine followed by a reduced-intensity conditioning and HSCT [80–81]. Schmid and coll. employed the FLAMSA regimen on 75 consecutive high-risk patients, 27 of whom affected by primary refractory AML and 22 by untreated relapse of AML, and reported a one-year non-relapse mortality of 33% and a 2-years DFS of 40%. This regimen also includes the use of prophylactic donor-leukocyte infusions (pDLI) in

the absence of Graft-Versus-Host Disease (GVHD). The authors describe a better survival in patients who experienced a mild chronic GVHD respect to no GVHD or severe GVHD [82].

The Baltimore group has pioneered Post-transplant Cyclophosphamide (PT-CY) on day +3 and +4 after the transplant in the context of haploidentical donor transplantation and it reduces the incidence of GVHD [83–86]. PT-CY prevents GVHD by killing alloreactive T cells of the donor and host origin with preservation of regulatory T cells; on the other hand, stem cells are protected by the drug because of their high level of aldehyde dehydrogenase which converts Cy to a non-toxic metabolite [87]. Since its advent, the transplant from a haploidentical donor has become one of the most commonly used alternative donor strategies. In the study by Ciurea et al. clinical outcomes of patients diagnosed with AML undergoing SCT from MUD or haploidentical donor with PT-CY were evaluated and overall survival resulted comparable in two groups with a lower incidence of GVHD in the haploidentical donor group [85]. The introduction of this strategy allowed even minor transplant centers to be able to perform haploidentical donor transplantation by omitting the need for ex vivo T cell depletion, which is an expensive procedure that requires dedicated laboratories. Because of the success demonstrated at preventing GVHD in the haploidentical setting, its role is now being also evaluated in the other settings—Matched unrelated donor, HLA identical donor [86, 88]—and it might be the strategy allowing calcineurin inhibitors and mTOR inhibitors-free GvHD prophylaxis [89].

Comparable results at preventing GVHD in the unmanipulated HSCT setting were obtained with another strategy based on the use of BM cells harvested from donors primed with low dose G-CSF (4 µg/kg/day) and on the administration of either MAC or RIC preparative regimen and an intensive GVHD prophylaxis consisting of a combination of five drugs: ATG, CSA, MTX, MMF and Basiliximab [90]. G-CSF stimulation increases the number of BM CD34⁺ cells [91] and has an intense immunoregulatory effect on BM T cells by down-regulating the expression of adhesion and CD28/B7 molecules and by favouring a T-cell shift from Th1- to Th2-type cells and inducing a higher production of IL-4 and IL-10 anti-inflammatory cytokines [92].

T-cell depletion to prevent GVHD remains an option in the haploidentical setting and the lack of extensive prospective studies comparing it with the unmanipulated graft transplantation leave the choice to the experience of the SCT center. This modality has been associated with a higher leukaemia relapse incidence - since T cells are responsible for the graft versus leukaemia effect - and higher TRM due to slower engraftment and a higher incidence of opportunistic infections [93]. New methods of graft manipulation have been developed in order to address these problems. A promising approach is the graft depletion of B cells and T cells carrying the $\gamma\delta$ chains of T cell receptor (TCR), being responsible for GVHD, while keeping $\alpha\beta$ T cells and Natural Killer (NK) cells that play an essential role in anti-tumour surveillance and the antiviral immunity (TCR $\gamma\delta$ /CD19 negative selection) [94]. A different strategy recently presented by the Perugia group is the infusion of donor regulatory T cells at day - 4 followed by the infusion of a megadose of CD34⁺ and conventional T cells on day 0 and no use of pharmacological post-transplant immunosuppression. This method resulted in a significant reduction in the incidence of leukaemia relapse, suggesting that regulatory T cells limit GVHD with no loss of GvL [95].

Disease recurrence remains the leading cause of treatment failure [96]. In order to reduce the RI post allogeneic stem cell transplantation (allo-SCT), studies including cellular therapies (DLI) [97, 98] and new drugs that seem to enhance the GvL effect like *FLT-3* inhibitors, immune checkpoint inhibitors [99] and epigenetic

therapies in the post-transplantation setting are ongoing. In the RICAZA trial azacitidine was administered for the first year after transplantation in 51 patients affected by AML undergoing allogeneic SCT and it showed a reduced risk of disease relapse [100].

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Conflict of interest

“The authors declare no conflict of interest.”

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References

- [1] Gupta V, Tallman MS, Weisdorf DJ. Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukaemia: myths, controversies, and unknowns. *Blood*. 2011
- [2] Tsirigotis P, Byrne M, Schmidt C et al. Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. *Bone Marrow Transplant*. 2016 Nov;.
- [3] Thanarajasingham G, Kim HT, Cutler C et al. Outcome and prognostic factors for patients who relapse after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013 Dec;.
- [4] Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European Leukemia Net AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated risk-adapted approach. *Nature Reviews. Clinical Oncology*. 2012a;9:579-590
- [5] Buccisano F, Hourigan C, Walter R. The prognostic significance of measurable ("Minimal") residual disease in Acute Myeloid Leukemia. *Curr Opin Malig Rep*. 2017
- [6] Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of _ AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017
- [7] Duarte R, Labopyn M, Bader P, et al. *Bone Marrow Transplant*. 2019:2019
- [8] Buccisano F, Maurillo L, Spagnoli A et al. *Blood*: Cytogenetic and molecular diagnostic characterization combined to post-consolidation minimal residual disease assessment by flow cytometry improves risk stratification in adult acute myeloid leukaemia; 2010
- [9] Zhou Y, Othus M, Araki D et al. Pre- and post-transplant quantification of measurable ("minimal") residual disease via multiparameter flow cytometry in adult acute myeloid leukaemia. *Leukemia* 2016;.
- [10] Buckley SA, Wood BL, Othus M, et al. Minimal Residual Disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukaemia: a meta-analysis. *Haematologica*. 2017
- [11] Mannis G, Martin TG III, Damon LE et al. Leuk Lymph: Long-term outcomes of patients with intermediate-risk acute myeloid leukaemia treated with autologous hematopoietic cell transplant in first complete remission; 2016
- [12] National Comprehensive Cancer Network clinical practice guidelines in oncology – Acute Myeloid Leukemia version 2014.
- [13] Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted. *Blood*: MRD-directed therapy for young adults with newly diagnosed acute myeloid leukaemia; 2019
- [14] Schuuruis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European Leukemia Net MRD Working Party. *Blood*. 2018
- [15] Walter R, Buckley S, Pagel JM et al. *Blood*: Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission; 2013
- [16] Quek L, Otto GW, Garnett C, et al. Genetically distinct leukemic stem cells in human CD34+ acute myeloid leukaemia are arrested at a hematopoietic precursor-like stage. *The Journal of Experimental Medicine*. 2016

- [17] Jongen-Lavrencic M, Grob T, Hanekamp D, Kavelaars FG, Al Hinai A, Zeilemaker A, Erpelinck-Verschueren CAJ, Gradowska PL, Meijer R, Cloos J, Biemond BJ, Graux C, van MarwijkKooij M, Manz MG, Pabst T, Passweg JR, Havelange V, Ossenkoppele GJ, Sanders MA, Schuurhuis GJ, Löwenberg B, Valk PJM. Molecular Minimal Residual Disease in Acute Myeloid Leukemia. *N Engl J Med*. 2018
- [18] Pratcorona M, Brunet S, Nomdede J et al.; Grupo Cooperativo Para el Estudio y Tratamiento de las Leucemias Agudas Mieloblasticas. Favourable outcome of patients with acute myeloid leukaemia harbouring a low-allele burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. *Blood*. 2013;
- [19] Gale RE, Green C, Allen C, et al. Medical Research Council Adult Leukaemia Working Party The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukaemia. *Blood*. 2008
- [20] Bazarbachi A, Bug G, Baron F, et al. Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukaemia patients with FLT3-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2020
- [21] Poiret X, Labopin M, Cornelissen JJ, et al. Outcome of conditioning intensity in acute myeloid leukaemia with monosomal karyotype in patients over 45-year-old: A study from the acute leukaemia working party (ALWP) of the European group of blood and marrow transplantation (EBMT). *American Journal of Hematology*. 2015
- [22] Poiret X, Labopin m, Maertens J et al. Allogeneic stem cell transplantation in adult patients with acute myeloid leukaemia and 17p abnormalities in first complete remission: a study from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). *J Hematol Oncol* 2017;
- [23] Poiret X, Labopin M, Polge E, et al. Allogeneic stem cell transplantation using HLA-matched donors for acute myeloid leukaemia with deletion 5q or monosomy 5: a study from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2020
- [24] Oliai C, Schiller G. How to address second and therapy-related acute myelogenous leukaemia. *British Journal of Hematology*. 2020;**188**:116-128
- [25] Sengsayadeth S, Labopin M, Boumendil A et al. Transplant Outcomes for Secondary Acute Myeloid Leukemia: Acute Leukemia Working Party of the European Society for Blood and Bone Marrow Transplantation Study. *Biol Blood Marrow Transplant* 24 2018
- [26] Schmaelter A-K, Labopin M, Socié G et al. Inferior outcome of allogeneic stem cell transplantation for secondary acute myeloid leukaemia in first complete remission as compared to de novo acute myeloid leukaemia. *Blood Cancer Journal* (2020).
- [27] Lancet TE, Uy GL, Cortes JE, et al. CPX-351 (Cytarabine and Daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukaemia. *Journal of Clinical Oncology*. 2018
- [28] Ferguson P, Hills RK, Grech A et al. An operational definition of primary refractory acute myeloid leukaemia allowing early identification of patients

who may benefit from allogeneic stem cell transplantation. *Haematologica* 2016 Nov;

[29] Jabbour E, Dayer N, Champlin R et al. Allogeneic stem cell transplantation as initial salvage therapy for patients with acute myeloid leukaemia refractory to high-dose cytarabine-based induction chemotherapy. *Am J Hematol* 2104;

[30] Schmid C, Schleuning M, Schwerdtfeger R et al. Long-term survival in refractory acute myeloid leukaemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. *Blood* 2006;

[31] Schmid C, Scheluning M, Ledderose G, et al. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukaemia and myelodysplastic syndrome. *Journal of Clinical Oncology*. 2005

[32] Gyurkoza B, Lazarus HM, Giralt S. Allogeneic hematopoietic transplantation in patients with AML not achieving remission: potentially curative therapy. *Bone Marrow Transplantation*. 2017

[33] Duval M, Klein JP, He W, et al. Hematopoietic stem cell transplantation for acute leukemia in relapse or primary induction failure. *Journal of Clinical Oncology*. 2010

[34] Christopeit M, Labopin M, Gorin N-C et al. Allogeneic stem cell transplantation following relapse post autologous stem cell transplantation in adult patients with acute myeloid leukaemia: a retrospective analysis of 537 patients from the Acute Leukemia Working Party of the EBMT. *Am J Hematol* 2018;

[35] Gillece MH, Labopin M, Savani BN, et al. Allogeneic haemopoietic transplantation for acute myeloid leukaemia in second complete remission: a registry report by the Acute Leukaemia Working Party of the EBMT. *Leukaemia*. 2020

[36] Halaburda K, Labopin M, Maillhol A, et al. Allogeneic stem cell transplantation in second complete remission for core-binding factor acute myeloid leukaemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2020

[37] Passweg JR, Labopin M, Christopeit M et al. Postremission Consolidation by Autologous Hematopoietic Cell Transplantation (HCT) for Acute Myeloid Leukemia in First Complete Remission (CR) and Negative Implications for Subsequent Allogeneic HCT in Second CR: A Study by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Biol Blood and Marrow Transplant* 26 2020

[38] Forman SJ, Rowe JM. *Blood: The myth of the second remission of acute leukemia in the adult*; 2013 Feb 14

[39] Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;

[40] Sorrow ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005

[41] Sorrow ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J ClinOncol*. 2014

[42] Roberto Raimondi, Alberto Tosetto, Rosi Oneto, Riccardo Cavazzina,

- Francesco Rodeghiero, Andrea Bacigalupo, Renato Fanin, Alessandro Rambaldi, Alberto Bosi; Validation of the Hematopoietic Cell Transplantation-Specific Comorbidity Index: a prospective, multicenter GITMO study. *Blood* 2012;
- [43] Gratwohl A. The EBMT risk score. Bone Marrow Transplantation. 2012
- [44] Martin Schmidt-Hieber, Myriam Labopin, Dietrich Beelen, Liisa Volin, Gerhard Ehninger, Jürgen Finke, Gerard Socié, Rainer Schwerdtfeger, Nicolaus Kröger, Arnold Ganser, Dietger Niederwieser, Emmanuelle Polge, Igor W. Blau, Mohamad Mohty; CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. *Blood* 2013;
- [45] Pierre Teira, Minoo Battiwalla, Muthalagu Ramanathan, A. John Barrett, Kwang Woo Ahn, Min Chen, Jaime S. Green, Ayman Saad, Joseph H. Antin, Bipin N. Savani, Hillard M. Lazarus, Matthew Seftel, Wael Saber, David Marks, Mahmoud Aljurf, Maxim Norkin, John R. Wingard, Caroline A. Lindemans, Michael Boeckh, Marcie L. Riches, Jeffery J. Auletta; Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. *Blood* 2016;
- [46] Tvedt THA, Hovland R, Tsykunova G, Ahmed AB, Gedde-Dahl T, Bruserud Ø. A pilot study of single nucleotide polymorphisms in the interleukin-6 receptor and their effects on pre- and post-transplant serum mediator level and outcome after allogeneic stem cell transplantation. *Clinical and Experimental Immunology*. 2018
- [47] Petersdorf EW. Genetics of graft-versus-host disease: The major histocompatibility complex. *Blood Rev*; 2013
- [48] M. Martin, D. Mann, and M. Carrington, "Recombination rates across the HLA complex: Use of microsatellites as a rapid screen for recombinant chromosomes," *Human Molecular Genetics*. 1995.
- [49] K. Fleischhauer and B. E. Shaw, "HLA-DP in unrelated hematopoietic cell transplantation revisited: Challenges and opportunities," *Blood*. 2017.
- [50] Tiercy J-M. Unrelated Hematopoietic Stem Cell Donor Matching Probability and Search Algorithm. *Bone Marrow Res*; 2012
- [51] Morishima Y et al. Biological significance of HLA locus matching in unrelated donor bone marrow transplantation. *Blood*; 2015
- [52] Pidala J et al. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. *Blood*; 2014
- [53] Lee SJ et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*; 2007
- [54] F. Lorentino *et al.*, "Comparative evaluation of biological HLA-DPB1 mismatch models for survival and graft versus host disease prediction after unrelated donor hematopoietic cell transplantation," *Haematologica*. 2020.
- [55] Crocchiolo R et al. Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation. *Blood*; 2009
- [56] Kollman C et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*; 2016

- [57] Y. J. Chang, L. Luznik, E. J. Fuchs, and X. J. Huang, "How do we choose the best donor for T-cell-replete, HLA-haploidentical transplantation?," *Journal of Hematology and Oncology*. 2016.
- [58] Saber W, Opie S, Rizzo JD, Zhang MJ, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. *Blood*; 2012
- [59] Gupta V et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood*; 2010
- [60] C. J. Lee *et al.*, "Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: A position statement from the acute leukemia working party of the European society for blood and marrow transplantation," *Haematologica*. 2017.
- [61] Aversa F et al. Successful engraftment of T-cell-depleted haploidentical 'three-loci' incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum. *Blood*; 1994
- [62] André-Schmutz I et al. Immune reconstitution without graft-versus-host disease after haematopoietic stem-cell transplantation: A phase 1/2 study. *Lancet*; 2002
- [63] Kunacheewa C, Ungprasert P, Phikulsod P, Issaragrisil S, Owattanapanich W. Comparative Efficacy and Clinical Outcomes of Haploidentical Stem Cell Transplantation to Other Stem Sources for Treatment in Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients: A Systematic Review and Meta-Analysis. *Cell Transplant*; 2020
- [64] Wagner JE et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: Influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood*; 2002
- [65] Brunstein CG et al. Alternative donor transplantation after reduced intensity conditioning: Results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*; 2011
- [66] Shouval R et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. *Lancet Haematol*; 2019
- [67] Bacigalupo A et al. Defining the Intensity of Conditioning Regimens: Working Definitions. *Biology of Blood and Marrow Transplantation*. 2009; **15**(12):1628-1633
- [68] Nagler A et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukaemia in remission: Comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus cy as conditioning regimen-A report from the acute leukaemia working. *Journal of Clinical Oncology*. 2013;**31**(28): 3549-3556
- [69] Bredeson C et al. Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. *Blood*. 2013;**122**(24):3871-3878
- [70] Rambaldi A et al. Busulfan plus cyclophosphamide versus busulfan plus

fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: An open-label, multicentre, randomised, phase 3 trial. *The Lancet Oncology*. 2015;**16**(15): 1525-1536

[71] Ben-Barouch S, Cohen O, Vidal L, Avivi I, Ram R. Busulfan fludarabine vs busulfan cyclophosphamide as a preparative regimen before allogeneic hematopoietic cell transplantation: Systematic review and meta-analysis. *Bone Marrow Transplantation*. 2016; **51**(2):232-240

[72] Eder S et al. Thiotepa-based versus total body irradiation-based myeloablative conditioning prior to allogeneic stem cell transplantation for acute myeloid leukaemia in first complete remission: A retrospective analysis from the Acute Leukemia Working Party of the Euro. *European Journal of Haematology*. 2016;**96**(1): 90-97

[73] Devine SM et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukaemia in first complete remission using a reduced-intensity conditioning regimen: Results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology). *Journal of Clinical Oncology*. 2015;**33**(35): 4167-4175

[74] Massenkeil G et al. Survival after reduced-intensity conditioning is not inferior to standard high-dose conditioning before allogeneic haematopoietic cell transplantation in acute leukaemias. *Bone Marrow Transplantation*. 2005;**36**(8):683-689

[75] Sébert M et al. Equivalent outcomes using reduced intensity or conventional myeloablative conditioning transplantation for patients aged 35 years and over with AML. *Bone Marrow Transplantation*. 2015;**50**(1):74-81

[76] Flynn CM et al. Reduced-intensity compared with high dose conditioning for allotransplantation in acute myeloid leukaemia and myelodysplastic syndrome: A comparative clinical analysis. *American Journal of Hematology*. 2007;**82**(10):867-872

[77] A. EP *et al.*, "Impact of Conditioning Regimen Intensity on Outcome of Allogeneic Hematopoietic Cell Transplantation for Advanced Acute Myelogenous Leukemia and Myelodysplastic Syndrome," *Biology of Blood and Marrow Transplantation*, vol. 12, no. 10, pp. 1047–1055, 2006.

[78] Ringdén O et al. Reduced-intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukaemia. *Journal of Clinical Oncology*. 2009;**27**(27): 4570-4577

[79] Scott BL et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukaemia and myelodysplastic syndromes. *Journal of Clinical Oncology*. 2017;**35**(11):1154-1161

[80] Malard F et al. Sequential Intensified Conditioning Regimen Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Intermediate- or High-Risk Acute Myeloid Leukemia in Complete Remission: A Study from the Acute Leukemia Working Party of the European Gr. *Biology of Blood and Marrow Transplantation*. 2017;**23**(2): 278-284

[81] Saure C et al. Upfront Allogeneic Blood Stem Cell Transplantation for Patients with High-Risk Myelodysplastic Syndrome or Secondary Acute Myeloid Leukemia Using FLAMSA-Based High-Dose Sequential Conditioning Regimen. *Biology of Blood and Marrow Transplantation*. 2012;**18**(3):466-472

- [82] Schmid C, Scheluning M, Ledderose G, et al. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukaemia and myelodysplastic syndrome. *Journal of Clinical Oncology*. 2005;**23**:5675-5687
- [83] Munchel A et al. Nonmyeloablative, HLA-haploidentical bone marrow transplantation with high dose, post-transplantation cyclophosphamide. *Pediatr. Rep.* 2011;**3**(2S):43-47
- [84] Kasamon YL et al. Nonmyeloablative HLA-Haploidentical Bone Marrow Transplantation with High-Dose Posttransplantation Cyclophosphamide: Effect of HLA Disparity on Outcome. *Biology of Blood and Marrow Transplantation*. 2010; **16**(4):482-489
- [85] Ciurea SO et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukaemia. *Blood*. 2015;**126**(8): 1033-1040
- [86] M. M. *et al.*, "Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation," *Blood*, vol. 127, no. 11, pp. 1502–1508, 2016.
- [87] Moreb JS. Aldehyde dehydrogenase as a marker for stem cells. *Current Stem Cell Research & Therapy* 2008 Dec;**3** (4):237–246. doi: 10.2174/157488808786734006. PMID: 19075754.
- [88] Moiseev IS et al. Graft-versus-Host Disease Prophylaxis in Unrelated Peripheral Blood Stem Cell Transplantation with Post-Transplantation Cyclophosphamide, Tacrolimus, and Mycophenolate Mofetil. *Biology of Blood and Marrow Transplantation*. 2016;**22**(6):1037-1042
- [89] L. Williams, F. Cirrone, K. Cole, M. Abdul-Hay, L. Luznik, and A. S. Al-Homsi, "Post-transplantation Cyclophosphamide: From HLA-Haploidentical to Matched-Related and Matched-Unrelated Donor Blood and Marrow Transplantation," *Frontiers in Immunology*, vol. 11. 2020.
- [90] Di Bartolomeo P et al. Haploidentical, unmanipulated, G-CSF-primed bone marrow transplantation for patients with high-risk hematologic malignancies. *Blood*. 2013;**121**(5): 849-857
- [91] Shier LR, Schultz KR, Imren S, Regan J, Issekutz A, Sadek I, Gilman A, Luo Z, Panzarella T, Eaves CJ, Couban S. Differential effects of granulocyte colony-stimulating factor on marrow- and blood-derived hematopoietic and immune cell populations in healthy human donors. *Biology of Blood and Marrow Transplantation* 2004 Sep;**10**(9):624–634. doi: 10.1016/j.bbmt.2004.05.009. PMID: 15319774.
- [92] Chang YJ, Zhao XY, Huo MR, Huang XJ. Expression profiles of adhesion molecules on naïve T cells in bone marrow grafts of healthy donors treated with granulocyte colony-stimulating factor. *Transplant Immunology*. 2009;**21**(4):228-233
- [93] Reisner Y, Hagin D, Martelli MF. Haploidentical hematopoietic transplantation: Current status and future perspectives. *Blood*. 2011; **118**(23):6006-6018
- [94] Airolidi I et al. $\gamma\delta$ T-cell reconstitution after HLA-haploidentical hematopoietic transplantation depleted of TCR- $\alpha\beta$ + /CD19+ lymphocytes. *Blood*. 2015;**125**(15):2349-2358
- [95] Martelli MF et al. HLA-haploidentical transplantation with regulatory and conventional T-cell adoptive immunotherapy prevents

acute leukaemia relapse. *Blood*. 2014;
124(4):638-644

[96] Cornelissen JJ *et al.*, "The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach", *Clin Oncol*. 2012.

[97] Jaiswal SR, Zaman S, Chakrabarti A, Sen S, Mukherjee S, Bhargava S, Ray K, O'Donnell PV, Chakrabarti S. Improved Outcome of Refractory/Relapsed Acute Myeloid Leukemia after Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation with Myeloablative Conditioning and Early Prophylactic Granulocyte Colony-Stimulating Factor-Mobilized Donor Lymphocyte Infusions. *Biol Blood Marrow Transplant*. 2016 Oct

[98] F. J. *et al.*, "Full donor chimerism without graft-versus-host disease: The key factor for the maximum benefit of pre-emptive donor lymphocyte infusions (pDLI)," *Bone Marrow Transplant.*, vol. 50, pp. S125–S126, 2015.

[99] Soiffer RJ, Davids MS, Bin Chen Y. Tyrosine kinase inhibitors and immune checkpoint blockade in allogeneic hematopoietic cell transplantation. *Blood*. 2018;**131**(10):1073-1080

[100] Craddock C *et al.* Tolerability and Clinical Activity of Post-Transplantation Azacitidine in Patients Allografted for Acute Myeloid Leukemia Treated on the RICAZA Trial. *Biology of Blood and Marrow Transplantation*. 2016;**22**(2):385-390