The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach

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Allogeneic stem cell transplantation for patients with AML in remission: an integrated risk adapted approach

A position paper from the European Leukemia Net (ELN) AML Working Party

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Running title: Risk adapted transplantation strategy.

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Abstract

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is frequently applied as part of treatment in acute myeloid leukemia (AML) in first or subsequent remission. It reduces relapse, but non-relapse mortality (NRM) and morbidity may counterbalance that beneficial effect. Here we review recent studies reporting new disease specific prognostic markers as well as alloHSCT related risk factors to be identified at specific time points during treatment. We propose risk assessment as a dynamic process during treatment, incorporating both disease and transplant related factors for the decision to proceed either to alloHSCT or with a non transplant strategy, whereby alloHSCT may be favored if projected disease free survival can be expected to be improved by at least 10%, based on individual risk assessment. Pivotal for such an approach are initial disease risk assessment, search for a sibling or unrelated donor early after diagnosis, and the incorporation of time dependent risk factors, all within the context of an integrated therapeutic management approach.

Introduction

Myeloablative allogeneic hematopoietic stem cell transplantation (alloHSCT) from an HLA-identical sibling donor is generally recommended for patients with acute myeloid leukemia (AML) in first complete remission (CR) without a favorable risk genetic profile (1-9). Although it offers a strong anti-leukemic effect, the benefit of alloHSCT in terms of overall survival is compromised by non-relapse mortality (NRM). As a consequence, alloHSCT may result in a substantial gain in disease free survival (DFS) and overall survival (OS) in a particular group of patients, but also in a loss of survival in other patients, despite significantly reducing relapse. Therefore, it is important to assess the most significant variables that affect the risk of relapse and variables predicting NRM at diagnosis, but also at later time-points during the course of treatment, as illustrated in Figure 1. The main questions to be addressed repeatedly for the individual patient during that process include:

1. Having obtained remission, to what extent does alloHSCT reduce relapse as compared to an alternative consolidation strategy in this particular type of leukemia?
2. How do alloHSCT and the non-transplant consolidation strategy compare with respect to NRM and also morbidities?
3. Combining the risks of NRM and relapse, what percentage of longterm DFS can be projected for the individual patient?
3. What are the prospects after relapse?

Combining the answers to these questions may yield an estimate to what extent the composite endpoint DFS may be improved and whether quality of life may be compromised. Here we review recent studies reporting new disease specific prognostic markers as well as alloHSCT related risk factors to be identified at specific time points during treatment. We propose risk

assessment as a dynamic process during treatment, integrating both disease and transplant related risks for the final decision in the individual patient to proceed either to alloHSCT or with a non transplant approach, aiming for a significant benefit in DFS of at least 10% by alloHSCT, which order of magnitude is based on earlier recommendations following large meta-analyses studies (4-6). Such an integrated approach would deviate from a "one size fits all" strategy and result in a more tailored approach for the individual patient.

Risk of the disease

Cytogenetic analysis has allowed for distinguishing categories of AML with widely different prognosis and risk of relapse. Three cytogenetic prognostic categories (favorable, intermediate, poor) have long been used. However, cytogenetic risk classification is continuously being refined (12), incorporating new categories such as e.g. the so-called monosomal karyotype (MK) category, which is associated with a very poor outcome and which is already used by several cooperative AML study groups (13). As a detailed review of cytogenetic abnormalities has been performed before, current cytogenetic abnormalities to be taken into account are summarized in Table 1 and presented according to prognosis. The listing is largely based on a recent summary by Grimwade et al (12) and the ELN-recommendations reported earlier (14).

Several larger donor versus no donor studies and their meta-analysis have shown that alloHSCT results in superior DFS and OS in patients with poor-risk AML in CR1. A meta-analysis of 5 earlier studies by Yanada et al had clearly shown improved DFS for patients with poor-risk cytogenetics, but the role of alloHSCT in intermediate risk AML proved less clear (4). The study performed by the HOVON/SAKK consortium, which also included a limited meta-analysis of the combined dataset of the HOVON/SAKK, MRC, EORTC and BGMT studies, showed

improved DFS in both intermediate and poor-risk patients (5). The reduction of relapse was estimated at approximately 50% (hazard ratio (HR) 0.4-0.5), as was derived from an intention to treat analysis. Although relapse was also significantly reduced in favorable risk patients with a risk of relapse below 35%, those patients did not benefit from myeloablative alloHSCT in terms of overall survival as a NRM of approximately 20% attenuated the beneficial effect of alloHSCT in those patients. These results were confirmed and extended in a larger meta-analysis by Koreth et al, including 18 prospective studies in AML CR1 (6). Although these older studies were confined to patients receiving myeloablative alloHSCT using sibling donors, the studies suggested that myeloablative alloHSCT may more generally be recommended for younger patients in first CR with intermediate or poor-risk cytogentic subtypes of AML, but not for patients with cytogenetic favorable subtypes of AML where the relapse probability is 35% or less. The latter applies to most patients with the so-called core binding factor leukemias—AML t(8;21), and AML inv(16)/t(16;16). Meanwhile, continued study of alloHSCT in intermediate risk AML is warranted, because of a continuous trend of progessiviely improved survival following autologous HSCT and/or chemotherapy as consolidation therapy (15-18).

The role of alloHSCT in the new very poor-risk MK subcategory has recently also been addressed (19-22). Although relapse after alloHSCT appeared high, 20% long term survival was reported and virtually no surviving patients were noted among CR patients receiving chemotherapy only or autologous transplantation. Strikingly, the relative reduction of relapse may not differ from what can be observed in other cytogenetic subtypes of AML (20), indicating that the immunotherapeutic effect of alloHSCT is exerted similarly among different AML categories and rather depends on alloreactive minor and major HLA-differences than on leukemia subcategory.

Molecular markers

The majority of patients with AML in first CR harbor an intermediate risk profile. While most of these leukemias lack a specific, prognostically relevant, karyotypic abnormality, molecular genetic markers such as gene mutations and deregulated gene expression can be identified in the majority and may be associated with a more specific prognosis (23, 24). Approximately 50% of cytogenetically normal AML may carry a mutation in the nucleophosmin gene (*NPM1*) (25). The prognostic value of the presence of the *NPM1* mutation appeared to depend on the additional presence of the internal tandem duplication (ITD) in the FLT3 tyrosine kinase receptor (*FLT3*/ITD) (26-29). Myeloid leukemia's characterized by the *NPM1* mutation but without *FLT3*/ITD, appeared to exhibit a more favorable prognosis with relapse rates less than 30%. Very similar to what was observed in cytogenetic favorable subgroups of AML, characterized by a relapse risk of less than 35%, a German study evaluating alloHSCT in molecularly defined subgroups of cytgenetically normal AML patients showed that patients with *NPM1* mutation but without *FLT3*/ITD did not benefit from alloHSCT due to enhanced NRM, while alloHSCT appeared associated with better survival in patients with the *FLT3*/ITD mutation in their series, although the relapse rate after alloHSCT may be higher as can be observed in intermediate risk AML patients (9-11). Also, the molecular subtype of AML based on the mutation of CEBPA appeared associated with a more favorable prognosis, whereby especially the subtype of AML characterized by a bi-allelic mutation appeared associated with a low risk of relapse (30-34). Therefore, it seems reasonable to withhold myeloablative allogeneic HSCT also in that category of AML patients. Although new molecular abnormalities associated with a better prognosis have been put forward, validation in independent cohorts of patients with mature follow-up are

required before incorporating these abnormalities in our decision making as regards allogeneic HSCT in CR1. Also new molecular markers have been identified that specifically relate to poor or very poor-risk AML, characterized by a very high risk relapse after attainment of first CR (Table 1). These categories for instance include AML with over expression of EVI-1 (35-37). Outcome of younger patients with EVI-1 AML appeared to be dismal, but recipients in CR1, who proceeded to allogeneic HSCT were suggested to benefit (37).

Response and residual disease

Apart from cytogenetic and molecular prognostic markers that are identified at diagnosis, a number of variables to be monitored during induction and consolidation therapy may offer additional prognostic information, which may affect the decision whether or not to proceed to alloHSCT. Such variables include time to CR, number of blasts early after induction and quantified minimal residual disease (MRD) after induction or consolidation (Table 1) (38). Different groups have shown that quantified levels of MRD relate to outcome and risk of relapse in first CR patients, although prospective validation studies are largely lacking. A study from Italy addressed the question whether multicolor flow cytometry (MFC) applied after induction and consolidation would allow to identify patients with a low risk of relapse < 30-35%, similar to the favorable risk AML subtypes as can be determined prior to the start of treatment by cytogenetics and/or molecular techniques (39). By combining the results of MFC obtained after induction and consolidation, a new subgroup of patients was identified with a favorable prognosis, for whom one may prefer to postpone alloHSCT until eventual relapse. One important caveat in those studies, however, is the effect of alloHSCT itself in that "new" good-risk group. If the majority of patients in that new subgroup actually received an alloHSCT and benefitted

from that modality, it may be hazardous to omit that treatment in the future without having shown favorable outcome of a substantial number of patients, who did not proceed to alloHSCT. In principle, that caveat applies to all studies claiming to identify a new subgroup of good-risk patients, which necessitates the prospective evaluation of risk-adapted treatment, including decisions based on MRD. Furthermore, the presence or absence of MRD before transplantation may provide important prognostic information (40). It may be argued that the presence of MRD identifies a subgroup of patients with a particularly high risk of relapse, thereby qualifying for alloHSCT even in prognostic favorable AML. Minimal residual disease may be quantified by MCF but also by PCR, including quantitative assays. PCR-based monitoring in cytogenetically defined low risk AML, in particular those exhibiting an inv(16) may identify patients with an increased risk of relapse, who then qualify for alloHSCT (41). In addition, the most frequent genetic aberration in AML, the *NPM1* mutation, can also be excellently monitored in a quantitative way, allowing to identify patients with a higher risk of relapse, for whom an alloHSCT may be considered (42, 43).

Predicting counterbalancing non relapse mortality (NRM)

As outlined above, there seems to emerge general agreement that NRM associated with myeloablative alloHSCT may outweigh a beneficial effect on relapse in patients with a cytogenetic favorable-risk profile, but with the advent of reduced intensity conditioning regimen as well the identification of the most important parameters predicting for NRM, a careful assessment of NRM-risk should complement the cytogenetic and molecular inventory of the risks associated with the leukemia in each patient. The HOVON analysis of sibling alloHSCT in 4 larger AML-studies (5) showed that age significantly predicted outcome, which effect was

mainly exerted by higher NRM in patients older than 40 years. Apart from age, other variables (Table 2) such as general performance, CMV serostatus, cytokine polymorphism, donor/recipient gender-combination, and comorbidities significantly predict for NRM (44). Taking important individual risk factors into account, composite risk scores were developed, including the European Group for Blood and Marrow Transplantation (EBMT) risk score and the Seattle hematopoietic cell transplantation comorbidity index (HCT-CI). The EBMT risk score is based on 5 criteria: disease stage, patient age, donor type, time interval from diagnosis to transplantation, and donor-recipient gender combination (45). The score was validated in several independent patient cohorts and confirmed over time. Recently, the score was also tested and validated in other hematological disorders, including AML (46). It was shown that AML patients in CR1 receiving myeloablative alloHSCT with a low risk-score ranging in between 0 and 1 point experienced a NRM of less than 15%, patients with scores 2-3 experienced a NRM of approximately 20-25%, and patients with higher risk scores (>4) showed enhanced NRM of approximately 35% (Figure 2, panel A). The risk score was initially conceived to assess NRM and survival. It had, however, also an impact on death from relapse. Loss of overall survival in patients with higher risk scores appeared to be due to both enhanced NRM and a higher relapse rate. Despite that limitation, its application in risk-assessment prior to transplantation appears clinically useful and is now quite widely accepted (47). Risk assessment for an individual patient is complicated as apart from pre-transplant parameters (44-48), also peri-transplant and post-transplant factors influence outcome (Table 2). Peri-transplant factors include the transplant techniques, conditioning regimen, GVHD prevention, and stem cell source (49). Post-transplant risk factors include the predominating factor GVHD, which needs to be assessed itself in terms of predisposing risks (50, see below). Pre-transplant risk factors generally exert additive effects,

but their impact may vary and depend on the sum of the risks. Survival is generally 3-5% worse for CMV seropositive patients compared to CMV seronegative patients, which effect is especially evident in EBMT low risk patients (46). In contrast, the role of Karnofsky performance score may become increasingly important with increasing EBMT risk score, and act independent from comorbidities present (51). Cytokine polymorphisms and single nucleotide changes within HLA locus have recently been described as factors associated with outcome, and may be integrated in risk assessment in the future (52).

Another composite risk-score is the HCT-CI, which was developed in Seattle. In earlier studies, the adapted Charlson comorbidity index predicted NRM, but that index lacked sensitivity (53, 54). Therefore, the hematopoietic cell transplantation (HCT) comorbidity index (CI), based on a number of comorbidities was developed (51, 53-57). A HCT-CI of, respectively, 0, 1 or 2 points resulted in a 2 yr NRM rate of approximately 10%, 15-20% and 25%. A higher CI score of 3 or $\geq$ 4 resulted in NRM rates of 35-40% (Table 3). A validation study showed the impact of the HCT-CI score on OS, NRM and RFS in both AML and MDS (57) patients. The HCT-CI was subsequently also confirmed in other institutions, different diagnoses, and in recipients of reduced intensity conditioning alloHSCT (58-61). A recent study in Spain also confirmed the score, but added more detail in patients with higher scores, enabling to identify subgroups in patients with a score exceeding 3 (62). Collectively, these studies have suggested that acceptable rates of NRM following alloHSCT can be expected in patients with a low EBMT score or with a low comorbidity score. Accordingly, by combining the risk of relapse and NRM (Table 4, Figure 1), it may be argued that patients, whose AML is characterized by a relapse risk > 50%, which may be reduced to less than 25% after alloHSCT, and for whom NRM can be estimated < 25%, those patients may be expected to benefit from alloHSCT by a difference in DFS of at least 10%

and therefore may qualify for alloHSCT. Likewise, a NRM of approximately 30% may still be acceptable in patients, whose leukemia is characterized by a very high risk of relapse (> 80%) (Table 4).

Meanwhile we would like to stress that transplant outcome continues to improve as a result of a number of developments (63-66), including better supportive care, quality management systems, more efficacious infection prophylaxis, and high resolution HLA-typing, which necessitates repeated validation and refinement of NRM risk scores. While it is beyond doubt that high resolution HLA typing has considerably improved matching between donor and recipient and thereby outcome (66), NRM following myeloablative unrelated donor alloHSCT may still be somewhat higher as compared to sibling alloHSCT. The risk of NRM progressively increases with the number of HLA disparities, emphasizing the importance of high-resolution HLA typing and the selection of donors with, preferably, no more than one mismatched allele out of 8 (67, 68). Currently, a number of cooperative groups have incorporated unrelated donor alloHSCT in their protocols for upfront treatment of AML patients, as multiple retrospective and prospective studies have shown that "well matched" unrelated donor grafts may be associated with acceptable NRM and strong reduction of relapse in AML CR1 patients (69-76). In the recent prospective study of the German Austrian AML Study Group, equivalent efficacy and NRM was shown in a head to head comparison of matched related and unrelated donor alloHSCT in adult high-risk patients (76). Collectively, these studies suggest that an unrelated donor alloHSCT is justified if the a priori risk of relapse is sufficiently high and the counterbalancing NRM following unrelated donor alloHSCT can be estimated as moderate. Given the time needed to identify and prepare for an unrelated donor alloHSCT, it implies that the search for a sibling and the subsequent search for an unrelated donor should be performed as soon as possible after

diagnosis and initial risk assessment. While the probability of identifying an adult unrelated donor may be as high as 60% for Caucasian patients, still a considerable number of patients with a diverse ethnic background lack a suitable donor. Alternative donors and/or stem cell sources include unrelated cord blood and haploidentical family donors (77-82). Currently, in many centers, such transplants are not routinely performed in patients with AML in first CR given the higher NRM associated with these donors/stem cell sources. However, first CR patients with a very high risk of relapse (> 80%) and lacking a sibling or unrelated donor may qualify for an alternative donor if the risk of NRM can be estimated not to exceed approximately 35%. Preferably, such transplants should be performed by experienced centers, that have validated these transplants with respect to NRM and anti-leukemic efficacy.

Non-myeloablative (MA) or reduced intensity conditioning (RIC) using sibling or matched unrelated donors in older AML patients or patients with comorbidities.

While alloHSCT has predominantly been studied in younger AML patients, AML predominantly affects older individuals (median age at diagnosis of 71 years (8)). Non-MA or RIC-regimen have been developed in order to reduce NRM in older or medically less fit patients, who do not tolerate a myeloablative conditioning regimen. Several studies have indeed shown that the morbidity and mortality following RIC alloHSCT are less than after MA-conditioning and that encouraging graft versus leukemia effects (GVL) are exerted (reviewed in 83-85, Figure 2 panel B). For the time being, no mature results from prospective, randomized studies comparing these two modalities have been reported in literature sofar. Most comparative studies reported were performed retrospectively and concerned patients with AML/MDS in CR1, CR2, or with advanced disease (86-95). During the prospective German-Austrian study (76), a growing

number of patients received RIC-regimens. Although not randomized, that study prospectively suggested equivalent results in patients receiving RIC or MA regimen in terms of relapse, NRM, and survival. However, several retrospective studies have meanwhile suggested a somewhat higher relapse rate in recipients of RIC alloHSCT and especially in recipients of non-MA alloHSCT (87, 95-97), although these studies relate to patients receiving different types of preceding induction and consolidation therapy, which may impact also on outcome after alloHSCT. Therefore, prospective comparative studies in similarly pretreated patients are highly needed and participation should be encouraged. Nevertheless, a recent prospective comparison of older AML patients by sibling donor availability suggested improved disease free survival for patients with a donor (98, 99). In addition, 2 recent large retrospective studies in older cohorts of AML patients also suggested improved outcome in recipients of RIC alloHSCT as compared to conventional chemotherapy (100, 101). Preferably, a prospective randomized comparison of alloHSCT from sibling or unrelated donors with chemotherapy as consolidation therapy should establish the long-term value of this approach, especially in older patients (Figure 1). Currently, such a prospective randomized study is being performed in Europe by the EBMT and several cooperative groups (ClinicalTrials.gov Identifier: NCT00766779).

Adverse effects beyond 2 years after transplantation and quality of life.

So far the decision whether or not to advice alloHSCT as consolidation therapy was discussed by weighing the counterbalancing risks of relapse at one hand and NRM at the other hand. While that discussion is underpinned with mature survival data from a number of studies, late, persistent morbidity and quality of life were not taken into account. However, this issue cannot be disregarded especially when chemotherapeutic approaches and/or autologous HSCT, which

are associated with less morbidity continue to improve outcome in intermediate risk AML (15-18). Several studies in recipients of alloHSCT have addressed the issue of late morbidity and late mortality occurring in patients, who were alive and well at 2 years after alloHSCT (102-106). A relative increase of 20% mortality, gradually occurring during the ensuing 2 decades, has been reported when comparing alloHSCT recipients with age matched controls. Late morbidities include: a long lasting immune deficiency, endocrine dysfunction; skeletal disorders; ocular problems, respiratory tract problems; salivary function and dental problems; liver complications; vascular complications; chronic kidney disease; sexuality; and secondary cancers (107-111), all adversely impacting on quality of life compared to conventional chemotherapy (111). While a detailed discussion of late morbidities and reduced quality of life goes beyond the scope of this review, it should be stressed that the major risk factor for most if not all these morbidities is chronic GVHD and the long lasting immunosuppressive therapy needed for its treatment. Probabilities to encounter each specific morbidity is still relatively low, but the incidence of chronic GVHD following RIC alloHSCT is considerable and a reliable risk estimate that predicts for chronic GVHD is strongly needed (112). A large study from Seattle estimated the risk of persisting GVHD with higher age, peripheral blood as a stem cell source, unrelated donor, and gender combination as the most important risk factors (113). While a reduction of quality of life may be incorporated quantitatively in the so-called “quality of life adjusted life years saved”, as was recently reported (114), the complicated quantifications are extremely difficult to convey and to discuss with individual patients, who may value the quality of his/her life on a very individual, personal basis.

Transplantation in second remission

Due to its potent anti-leukemic effects, alloHSCT has consistently been considered as the treatment of choice for most relapsed patients. Outcome of allografts beyond first remission, however, is inferior to that in first-remission patients, owing to an increase in both treatment-related mortality (25%-35%) and relapse (40%-45%). Breems et al reported a prognostic index for adult patients with relapsed AML based on a cohort of 667 AML patients in first relapse (115). Four relevant parameters significantly predicted for outcome, including length of relapse free interval, age at relapse, cytogenetics at diagnosis, and whether or not patients had received a previous transplantation. Based on these parameters, 3 risk groups could be defined. In all 3 groups, recipients of an alloHSCT faired better than patients treated with chemotherapy or an autograft. However, only 249 out of 667 (37%) relapsing patients entered second CR and less than 50% of those CR2 patients proceeded to allografting (n=109), indicating that ultimately only 15% of relapsed patients received the preferred treatment option. More recent observations were reported by Kurosawa et al (116) and by Armistead (117), who detailed results from 599 relapsing patients treated at MD Anderson. Given the restricted application of alloHSCT in CR2 and in view of the dismal outcome in patients, who did not proceed to alloHSCT, allografting would therefore preferentially need to be considered and weighed in patients in first CR (Figure 1).

Conclusion

It has become clear that the decision whether or not to apply alloHSCT in AML patients no longer depends alone on the risk-profile of the leukemia and the availability of a donor. The decision making process has become more complex by also taking into account patient specific parameters that predict for NRM. Table 4 shows a condensed proposal how to integrate the most

important risk factors for decision making, whereby we would suggest to favor alloHSCT as consolidation therapy in AML CR1 only if an advantage in DFS of at least 10% may be expected, as can be deduced from the individual risks of relapse and NRM. A continuous risk assessment of the disease in parallel to risk assessment of the transplant procedure is considered pivotal as well as an early search for a donor and stringent cooperation between the leukemia care providers and the transplant teams and unrelated donor registries in the respective countries. While such an integrated system may provide a more tailored approach for the individual patient,, the strategy as such should be subject of ongoing prospective study..

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Table 1. Prognostic factors in AML (leukemia related)

	type of parameter		
Effect	cytogenetic	molecular	clinical
Favorable	t(8;21) inv(16)/t(16;16) t(15;17)	mutated *CEBPA* (double) mutated *NPM1* (without *FLT3*/ITD)	MRD negative
Adverse	inv(3)/t(3;3) t(9;22) t(9;11) t(6;9) -5 or del(5q) -7 abn(17p) complex karyotype monosomal karyotype	enhanced Evi-1 expression *MLL*-rearranged *FLT3*-ITD mutation mutated *DNMT3A* expression of BAALC expression of ERG expression of MN1 *WT1* polymorphism *BCR/ABL positive*	increasing age high WBC extramedullary disease no early CR persistent MRD CD34 positive t-AML

Abbreviations: AML, acute myeloid leukemia; CEBPA, CCAAT/enhancer binding protein; NPM1, nucleophosmin; FLT3-ITD, fms-like tyrosine kinase receptor-3 - internal tandem duplications; Evi-1, ecotropic viral integration site 1; WBC, white blood cells; MLL, mized lineage

leukemia; CR, complete remission; DNMT3A, DNA methyltransferase 3A; MRD, minimal residual disease; BAALC, gene for Brain and acute leukemia, cytoplasmic. ; ERG, Ets-related gene; MN1, meningioma-1; WT1, Wilms tumor 1; t-AML, treatment related AML

Table 2. Prognostic factors for NRM

	AlloHSCT-parameter assessed at timepoint		
Effect	pre-transplantation	peri-transplantation	post-transplantation
Favorable	sibling donor (HLA-matched) shorter time from diagnosis to transplant* Caucasian race	non-myeloablative conditioning stem cell source (BM/PB) (T-cell depletion)	early immune recovery
Adverse	higher recipient age* recipient/donor sex* co-morbidities (HCT-CI) CMV serostatus cytokine polymorphism unrelated donor HLA-mismatch performance score refractory leukemia t-AML	myeloablative conditioning regimen alternative stem cell source (UCB)	graft-versus-host disease severity

*factors incorporated in EBMT-risk scrore

Abbreviations: NRM, non-relapse mortality; alloHSCT, allogeneic hematopoietic stem cell transplantation; HLA, human leukocyte antigen; PB, peripheral blood; BM, bone marrow; UCB, umbilical cord blood; HCT-CI, hematopoietic cell transplantation comorbidity index; CMV, cytomegalovirus; t-AML, therapy related AML

Table 3. Non-relapse mortality at 2 yrs according to HCT-Comorbidity Index (55, 56)*

Study	Non-relapse mortality (%) by HCT-CI		
	0	1-2	≥ 3
Sorror et al. (55)			
training set (n=708)	9	14-27	41-43
validation set (n=346)	14	19-22	40-41
Sorror et al. (56) (FHCRC n=177, MDACC n=67)	7	19-21	27-37

*The studies included both recipients of matched sibling or matched unrelated donor grafts following either myeloablative or NMA conditioning;

Abbreviations: HCT-CI, hematopoietic cell transplantation-comorbidity index; FHCRC, Fred Hutchinson Cancer Research Center; MDACC, MD Anderson Cancer Center

Table 4. Patient specific, integrated risk-based application of alloHSCT in AML CR1*

AML-risk Group**	AML Risk assessment, including respons to induction-I	Risk of relapse following consolidation by		Consider alloHSCT **if** continued CR after consolidation and **if** NRM-prognostic scores indicate:		
		Chemo/ autoPBSCT	alloHSCT	EBMT-score	HCT-CI score	NRM
Good	t(8;21), WBC ≤20 Inv(16)/t(16;16) *CEBPA*+ *FLT3*-ITD-/*NMP1*+, and CR1, and no MRD	35-40%	15-20%	NA (≤ 1)	NA (<1)	10-15%
IM	T(8;21), WBC ≤20 CN – X – Y, WBC ≤100, and CR	50-55%	20-25%	≤ 2	≤ 2	<20-25%
Poor	Good/IM, but no CR CN –X – Y, WBC >100 CA	70-80%	30-40%	≤ 3/4	≤ 3/4	<30%
Very poor	MK+ Abn3q26 EVI1+	>90%	40-50%	≤ 5	≤ 5	<40%

Abbreviations: alloHSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; CR, complete remission; NRM, non-relapse mortality; EBMT, European group for blood and marrow transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; NA, not advocated; CEBPA, CCAAT enhancer-binding protein alpha; FLT3ITD, fms-like tyrosine kinase receptor-3 - internal tandem duplications; NMP1, nucleair matrix protein; MRD, minimal residual disease; IM, intermediate; WBC, white blood cells; CBF, core binding factor; MK, monosomal karyotype, Evi-1, ecotropic viral integration site .

*The proposed patient specific application of alloHSCT in AML CR1 integrates the individual risks for relapse and NRM and aims for a DFS benefit of at least 10% for the individual patient as compared to consolidation by a non-alloHSCT approach

**The categorization of AML based on cytogenetic, molecular, and clinical parameters (including WBC) into good, intermediate, and (very) poor subcategories is subject of continuing study and debate. Here, categories are, arbitrarily, presented according to the latest HOVON/SAKK policy (www.HOVON.nl).

Legends to Figures

Figure 1.

Diagnostic and time-dependent parameters predicting for outcome after allogeneic stem cell transplantation versus alternative consolidation therapy in patients with acute myeloid leukemia in first complete remission, who undergo upfront treatment by induction and consolidation therapies.

Figure 2.

Cumulative incidence of non relapse mortality, with relapse as competing risk, in AML CR1 patients having received myeloablative alloHSCT (panel A) or reduced intensity conditioning RIC) alloHSCT (panel B) in Europe between 2000 and 2010, as determined by the EBMT risk score, including the parameters patient age, donor type, time interval from diagnosis to transplantation, and donor-recipient gender combination (according to reference 46 and by courtesy of the Acute Leukemia Working Party (ALWP) of the EBMT). Patients receiving RIC alloHSCT were significantly older then patients receiving myeloablative alloHSCT (median age (range): 38 years (35-77) versus 56 (54-77), p,0.0001).

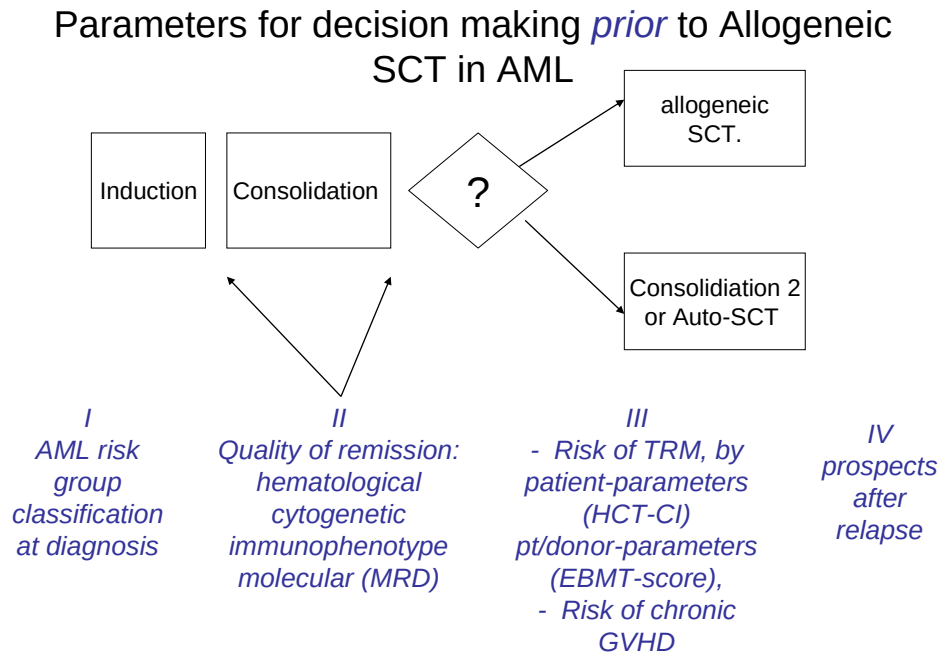
Parameters for decision making *prior* to Allogeneic SCT in AML
Induction
Consolidation
?
allogeneic SCT.
Consolidiation 2 or Auto-SCT
I
AML risk group classification at diagnosis
II
Quality of remission: hematological cytogenetic immunophenotype molecular (MRD)
III
- Risk of TRM, by patient-parameters (HCT-CI) pt/donor-parameters (EBMT-score),
- Risk of chronic GVHD
IV
prospects after relapse

Figure 1

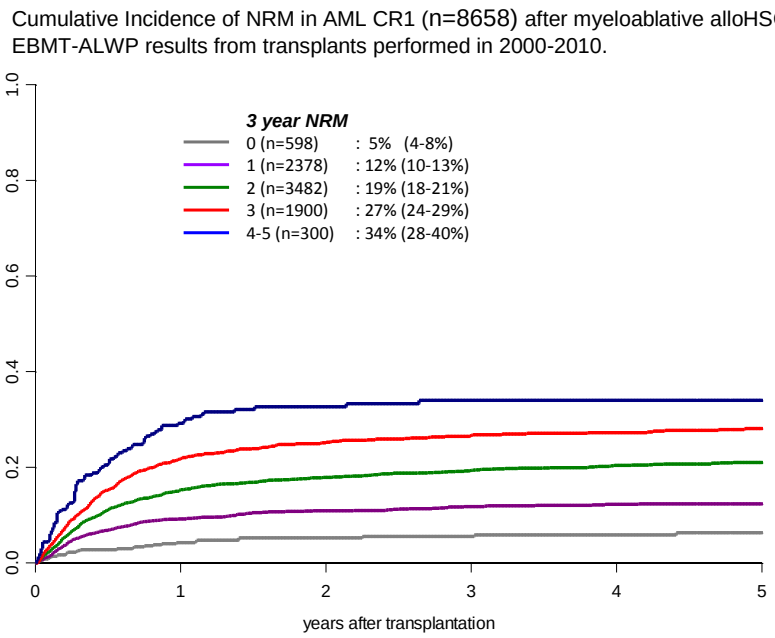

Figure 2 panel A

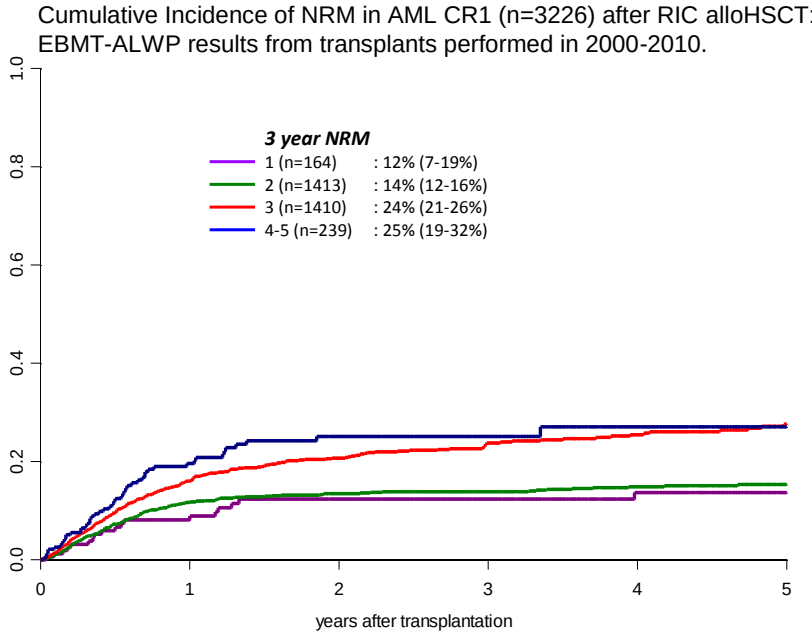

Figure 2 panel B