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Outcome and risk factor analysis of molecular subgroups in cytogenetically normal AML treated by allogeneic transplantation

Running Head: Role of molecular subgroups in HSCT for CN-AML

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Key points

- In AML with normal cytogenetics, age, response to induction, and *FLT3*-ITD allow for an estimate of outcome after allogeneic HSCT in CR1

- Neither variation of classical transplant techniques, nor development of cGvHD outweighs the negative impact of *FLT3*-ITD

Abstract

Patients with cytogenetically normal acute myeloid leukemia (CN-AML) can be subdivided by molecular mutations. However, data on the influence of combinations of different aberrations on outcome after allogeneic hematopoietic stem cell transplantation (HSCT) is limited. Therefore, we performed a retrospective registry analysis on 702 adults with CN-AML undergoing HSCT in first complete remission (CR). Patients were grouped according to presence or absence of *NPM1* mutations (*NPM1*^{mut}) and *FLT3* internal tandem duplications (*FLT3*-ITD). Double negative patients were evaluated for mutations of the *CCAAT*/enhancer binding protein α gene (CEBPα). The influence of genotypes on relapse, non-relapse mortality, leukemia-free survival (LFS) and overall survival (OS), and a prognostic classification combining NPM1/*FLT3*-ITD profile and classical risk factors were calculated. 2y-OS from HSCT was 81±5% in *NPM1*^{mut}/*FLT3*^{wt} (n=68), 75±3% in *NPM1*^{wt}/*FLT3*^{wt} (n=290), 66±3% in *NPM1*^{mut}/*FLT3*-ITD (n=269) and 54±7% in *NPM1*^{wt}/*FLT3*-ITD (n=75; p=0.003). Analysis of *CEBPα* among patients with *NPM1*^{wt}/*FLT3*^{wt} revealed excellent results both in patients with *CEBPα*^{mut} (n=13, 2y-OS:100%), and with a triple negative genotype (n=138, 2y-OS:77±3%). In a Cox-model of predefined factors, older age, presence of *FLT3*-ITD and >1 course of chemotherapy to reach CR were associated with inferior outcome. 2y-OS/LFS were 88±3%/79±4% in patients without any, 77±2%/73±3% with one, and 53±4%/50±4 with>=2 risk factors (p=0.002 for LFS, p=0.003 for OS). Hence, *FLT3*-ITD proofed to be the decisive molecular marker for outcome after HSCT for CN-AML in CR1, regardless of *NPM1* mutational status, variations of transplant protocols, or development of GvHD. Age, *FLT3*-ITD and response to induction chemotherapy allow for a prognostic risk classification.

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) offers a strong antileukemic effect in acute myeloid leukemia (AML), although the benefit in terms of overall survival is compromised by non-relapse mortality (NRM).[1] In first complete remission (CR1), the indication for alloHSCT is frequently based on genetic risk factors. In general, transplantation is recommended for patients with unfavorable cytogenetics, and discouraged for patients with favorable cytogenetic aberrations, whereas data are less clear in the intermediate cytogenetic subgroup.[2;3;3]

In patients with intermediate cytogenetics, and particularly cytogenetically normal AML (CN-AML), molecular aberrations play a decisive role in prognosis.[2;4-7] Therefore, international guidelines recommend testing for the two most frequent molecular markers (i.e., the mutation of the nucleophosmin1 gene, *NPM1*^{mut}, and internal-tandem duplication of the fms-related tyrosine kinase 3 gene, *FLT3*-ITD), as well as the mutations of the *CCAAT*/enhancer binding protein α gene (*CEBPα*), as part of routine diagnostics in newly diagnosed AML.[2] Among other factors, the indication for alloHSCT in CN-AML achieving CR is frequently based on the molecular profile, in particular on the presence of an *FLT3*-ITD, although data on the role of alloHSCT even in this particular subgroup remains controversial,[5;8-11] and the negative prognostic value of this aberration is maintained in the allogeneic setting.[12] Recent data suggests that the mutual interaction of co-occurring molecular aberrations, rather than one single aberration alone, might be decisive for clinical outcome. In particular, the prognostic significance of *FLT3*-ITD is thought to be modified by *NPM1*^{mut}.[13-15] Nevertheless, it is not clear so far from clinical data, whether patient subgroups characterized by different combinations of molecular markers do have different outcomes after alloHSCT, since the numbers of transplanted patients in reported series are relatively small.[5;11;16] With this background, the Acute Leukemia Working Party (ALWP) of

EBMT performed a retrospective, registry based analysis, in order to provide data on risk factors and overall survival (OS) after alloHSCT in CR1 in large, molecularly defined subgroups of patients with CN-AML.

Patients and Methods

Inclusion criteria and data collection

EBMT is a voluntary organization including more than 500 transplantation centers, that are required to file annual follow-up reports on all consecutive HSCT, based on patients' written informed consent in accordance with the Declaration of Helsinki. After approval by the Acute Leukemia Working Party board, adult patients with de novo AML were selected from this database according to the following criteria: (1) first alloHSCT in CR1 (excluding CR with incomplete recovery, CRi) between 2006 and 2012 (2) HLA-identical related or at least 7/8 antigen (HLA A, B, DR, DQ) matched unrelated donor (RD/MUD) (3) normal karyotype and (4) available information on the presence or absence of *NPM1*^{mut} and *FLT3*-ITD at time of diagnosis. Cytogenetics and molecular genetics were performed by the referring institutions according to local standards.

Data extracted from the database and completed by transplant centers upon additional request included age, gender, donor relationship and HLA compatibility, conditioning regimen, graft source, graft-versus-host disease (GvHD) prophylaxis, disease response, incidence of GvHD and relapse after HSCT, survival status, date and cause of death, and last follow-up. In order to ensure quality of the data, physicians reviewed submitted data and made personal contact with reporting centers to clarify doubtful information.

Definitions and statistics

Remission and relapse,[2] conditioning intensity[17] and Graft-versus-Host Disease (GvHD)[18] were defined and classified as described.

The probabilities of acute and chronic GVHD, NRM, and relapse were calculated by using the cumulative incidence estimator to accommodate competing risks. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For acute and

chronic GVHD, death without the event was the competing risk. The Gray test was used for comparisons. Overall survival (OS) and leukemia free survival (LFS) were calculated from date of HSCT, using Kaplan-Meier estimates. For all prognostic analyses, continuous variables were categorised and the median was used as a cut-off point. Chronic GvHD was included as time dependant variable. A Cox proportional hazards model was used for multivariate regression. Variables differing in term of distribution between the groups and factors conceptually important were included in the model. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI).

All tests were two-sided. The type I error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. SPSS 19.0 and R 3.0.1 software packages were used.

Results

Information on molecular markers was available in 702 patients. Data on 15 patients reported earlier[12] were updated for the present analysis, whereas results in 687 patients had not been analyzed before. Median age was 51 years, 80% received PBSC grafts. 55% each had related, 45% had unrelated (8/8 match, n=49, 10/10 match, n=225, 9/10, n=49) donors. Conditioning was myeloablative (MAC) in 47%, and reduced (RIC) or non-myeloablative (NMA) in 53%. Based on the presence of *NPM1*^{mut} and *FLT3*-ITD at diagnosis, patients were grouped into four different genotypes: *NPM1*^{wt}/*Flt3*^{wt} (n=290, 41%), *NPM1*^{mut}/*FLT3*^{wt} (n=68, 10%), *NPM1*^{wt}/*FLT3*-ITD (n=75, 11%), and *NPM1*^{mut}/*FLT3*-ITD (n=269, 38%). Molecular subgroups were well balanced with respect to the majority of characteristics. However, imbalances were observed concerning the interval from diagnosis to CR (nine days longer in the *NPM1*^{wt} groups) and to alloHSCT (ten days longer in *FLT3*^{wt} groups), the number of induction courses to reach CR1 (higher in the *NPM1*^{wt}/*FLT3*-ITD group), the year of transplantation (one year earlier in the *FLT3*^{wt} groups), and the intensity of the conditioning (more MAC in the *FLT3*-ITD groups; cf. Table 1 for detailed patient characteristics).

Relapse and non-relapse mortality after alloHSCT

Concerning cumulative incidence of relapse (CIR), the molecular subgroups differed significantly according to *FLT3* mutational status, with patients with *FLT3*-ITD showing a higher CIR (26±3% and 34±6% at 2 years in patients with and without concomitant *NPM1*^{mut}) as compared to patients lacking *FLT3*-ITD (2-year CIR: 16±3% and 14±2% in patients with and without *NPM1*^{mut}, global p-value between *FLT3*-ITD and *FLT3*^{wt}: 0.0009). In contrast, the presence or absence of *NPM1*^{mut} did not significantly influence CIR in both

FLT3-ITD and *FLT3*^{wt}. Molecular subgroups did not show any influence on NRM (global p-value: 0.75;, Figure 1, supplement Table 1).

In the multivariate model, *FLT3*-ITD (HR:2.23, 95%CI:1.44-3.46, p=0.0003) and the number of courses of induction chemotherapy to reach CR1 (HR:1.50, 95%CI:1.02-2.22, p=0.04) showed significant influence on CIR, whereas variations of the transplant procedure such as donor choice, (sibling versus unrelated), intensity of the conditioning, TBI and use of ATG had no influence. Younger age (HR:3.42, 95%CI:1.98-5.91, p<0.0001), RIC (HR:0,.57, 95%CI:0.34-0,97, p=0.04) and a shorter interval between achievement of CR and date of alloHSCT (HR:0.55, 95%CI:0.34-0.90, p=0.02), but not molecular subtype, intensity of the conditioning, or donor type (including 1 AG mismatched unrelated donors) were protective against NRM (Table 2).

GvHD

Cumulative incidence of aGvHD grade 2-4 and cGvHD was 29±2% and 40±2%, respectively, with no differences among molecular subgroups (global p-value: 0.23 for aGVHD, 0.27 for cGvHD, see supplement Table 1 for details). No significant influence of cGvHD on CIR could be detected either in the entire cohort or within molecular subgroups (p=0.30/0.20 among *FLT3*^{wt} +/- *NPM1*^{mut}, 0.90/0.96 among *FLT3*-ITD+/- *NPM1*^{mut}), when including cGvHD into the model as time-dependent variable.

Overall survival and leukemia-free survival after alloHSCT

With a median follow-up of 26 months from transplantation among survivors, 2y-OS and LFS for the entire cohort was 70±2% and 64±2%, respectively. Molecular subgroups had a strong influence on outcome (global p-value 0.003 for OS, 0.002 for LFS), with the best outcome observed in the *NPM1*^{mut}/*FLT3*^{wt} group (2y-OS:81±5% LFS:75±5%). Notably,

NPM1^{wt}/*FLT3*^{wt} patients showed similarly favorable results (2y-OS:75±3% LFS:70±3%), whereas outcome was clearly inferior in patients harboring an *FLT3*-ITD (2y-OS:66±3%/LFS:60±7% in *NPM1*^{mut}/*FLT3*-ITD and 54±7%/48±7% in *NPM1*^{wt}/*FLT3*-ITD). Thus, in the presence of *FLT3*-ITD, *NPM1*^{mut} showed a positive trend, but did not significantly alter outcome results (p=0.15 for OS, p=0.13 for LFS, respectively; Figure 2A, LFS, B, OS; supplement Table 1).

Using a Cox model for multivariate analysis, the presence of an *FLT3*-ITD (HR:1.85, 95%CI:1.29-2.66, p=0,001 for OS, HR: 1,77, 95%CI: 1,27-2,48, p=0,001 for LFS) and age above the median (HR:2.54, 95%CI:1.77-3.66 , p<0,0001 for OS, HR:1.90, 95%CI:1.36-2.66 , p=0.0002 for LFS) were the main risk factors for outcome. Further, the number of induction courses to reach CR1 was of borderline significance (HR:1.37, 95%CI:0.99-1.91, p=0.06 for OS, HR:1.43, 95%CI:1.06-1.95, p=0.02 for LFS; Table 2). As with CIR, outcome was not influenced either by modifications of the transplant regimen (including donor type, donor match and intensity of the conditioning) or development of GvHD.

Impact of mutated CEBPα among double negative (NPM1^{wt}/Flt3^{wt}) patients

To further subdivide the NPM1^{wt}/Flt3^{wt} cohort, the role of the mutational status of CEBPα was analyzed in 151 informative patients. Thus, 2y-OS/LFS among triple negative patients (n=138, 91 %) was 77±3%/72±3%, whereas 13 patients (9%) harboring a CEPBα mutation had an OS/LFS of 100%/92±3% .

Prognostic risk classification

Based on the three independent risk factors (*FLT3*-ITD, age above the median, >1 induction course to reach CR1), a prognostic classification for outcome of CN-AML after

alloHSCT was developed. Outcome parameters were significantly influenced by the score (none vs. one vs. two or three factors; p=0.003 for OS, 0.002 for LFS, 0.0002 for CRI, 0.01 for NRM; Table 3; Figure 3). The classification was then validated in an independent cohort of an earlier study from our group.[12] Although the two cohorts differed significantly with respect to important variables (e.g. intensity of the conditioning, year of transplant, length of follow up), the prognostic value of the classification was confirmed (p<0.0001 for LFS, OS and CIR, respectively).

Discussion

In the largest study presented so far on the role of molecular markers in adult CN-AML patients undergoing alloHSCT in CR1, significant differences among genetic subgroups were observed. Thus, in addition to patient age, *FLT3*-ITD, but not *NPM1*^{mut}, was identified as decisive factor for outcome. NRM and GvHD were not influenced by the molecular profile. By providing data on OS in high numbers of recently transplanted patients, including both related and unrelated donor, as well as reduced and myeloablative transplants, the results firmly establish, which outcome can be expected after alloHSCT in different molecular subgroups of CN-AML. Given the fact that leukemia relapse as the decisive event for outcome after allo HSCT for AML was observed at a median of <6 months from alloHSCT both after RIC and MAC transplants,[19-21] a follow-up longer than 2 years seemed to be reasonable. Further, the data allowed for a prognostic classification of patients undergoing HSCT for CN-AML.

Strict inclusion criteria and an extensive survey among participating centers, including repeated questionnaires and personal contacts, ensured high patient numbers and data quality. Nevertheless, the nature of a retrospective, registry-based study implicates limitations.

First, EBMT registry only provides data on patients who in fact underwent alloHSCT. Therefore we are not able to answer the question of whether or not alloHSCT should be offered to all patients diagnosed with CN-AML and one of the molecular subgroups defined here.

Second, we could not determine the mutant/wildtype allele ratio (AR) of *FLT3*-ITD, nor the insertion site of *FLT3*-ITD, in the majority of patients. Both variables have been described to play a major role for outcome after conventional therapy and alloHSCT, and also seemed to

modify the role of other mutations, such as *NPM1*^{mut}.[16;22-24] However, heterogeneity, methodological problems and the relatively low sensitivity of most PCR assays, as well as a missing general agreement concerning a cutoff level for the *FLT3*-ITD/wildtype AR[11;16;23-27] have prompted the suggestion to generally classify all non-APL *FLT3*-ITD cases as poor risk.[10;28] Further, no role of the mutant/wildtype AR on CIR after alloHSCT could be shown by the recent AML-SG study,[11] and next generation sequencing revealed the presence of different *FLT3*-ITD clones within the same patient both at diagnosis and during the course of the disease.[29;30] Therefore, and in accordance with several well accepted prognostic models[3;5;31] and recent classification systems[7] for CN-AML, we decided to limit our analysis to the general presence or absence of *FLT3*-ITD.

Third, we don't have data on other, recently identified mutations possibly modifying the prognostic role of both *FLT3*^{wt} and *FLT3*-ITD patient subsets, such as *TET2*, *DNMT3A*, *ASXL1* and *IDH1/2*. The prognostic role and mutual interaction of these mutations is a matter of ongoing research,[32] and the role of different genotypes might vary according to the applied therapy, as shown for high-dose daunorubicin.[7] Further, integration of several mutations into a clinically based prognostic scoring system is difficult, as demonstrated in a recent study by the German AML-SG, where high numbers of missing data on concurrent mutations precluded the inclusion of these variables in a multivariable model on outcome.[11] Hence, for the time being, the data in molecular subgroups, which are based on the two most frequent molecular markers, as well as the proposed prognostic classification, might be a reasonable tool to estimate the outcome after alloHSCT in CR1 in a given patient with CN-AML.

The role of the general presence of *FLT3*-ITD for LFS and CIR even after alloHSCT has been shown previously for patients undergoing myeloablative conditioning for predominantly matched sibling transplants,[12] although it had not been observed by

others.[9;33] Besides confirming the negative influence of *FLT3*-ITD in a larger cohort including unrelated transplants and RIC, and extending it to an analysis on OS, we also looked for variations within the transplant procedure to identify strategies for improvement in this high-risk cohort. However, when adjusting for confounding factors, neither an unrelated donor, modified intensity of the conditioning, nor the use of ATG or inclusion of TBI into the preparative regimen could be shown to cause a significant difference among patients with *FLT3*-ITD. Similarly, development of cGvHD did not significantly protect against relapse. Hence, it seems unlikely, that the negative prognostic value of *FLT3*-ITD might be abrogated by modification of the traditional components of the transplant procedure. This strongly argues in favor of the integration of innovative approaches into the transplant strategies. As an example, *FLT3* inhibitors, which have been studied either as part of the induction treatment,[34-36] as bridging to alloHSCT,[(summarized in 28)] or as maintenance after alloSCT, should be further evaluated in randomized trials in order to improve outcome in this subgroup of patients.

As shown earlier,[5;37] *NPM1*^{mut} defined a subgroup with excellent prognosis among patients with *FLT3*^{wt}. In the context of alloHSCT, this is ascribed to the presence of a particular strength of the allogeneic immune response.[38] In contrast, the previously described protective role of *NPM1*^{mut} in patients bearing *FLT3*-ITD[13-15] could not be unequivocally confirmed by our data. Hence, this co-occurrence might either play no major role after alloHSCT, or the influence of *NPM1*^{mut} might be limited to patients with a low *FLT3*-ITD/wild type AR.[16;24] However, in a recent AML-SG study, no impact of a concurrent *NPM1* mutation could be demonstrated either.[11] Integrated genetic profiling data further revealed a modification of the prognostic role of *FLT3*-ITD by other mutations not evaluated in our study, e.g. TET2 or DNMT3A.[7]

Patients with a double negative genotype (*NPM1*^{wt}/*FLT3*^{wt}) were further characterized by presence or absence of *CEBP*α, the third molecular aberration generally recommended for testing in newly diagnosed AML.[2] Accordingly, even triple negative patients (n=138) showed an excellent outcome after alloHSCT, although having been identified to bear an increased risk in earlier studies.[5] This confirms data suggesting a potent Graft-versus-Leukemia effect in this particular subgroup.[39] Longer follow up might be required to confirm this observation, since this subgroup was the only one showing late relapses beyond 3 years from HSCT. In contrast, the excellent outcome of 13 patients with *NPM1*^{wt}/*FLT3*^{wt} and mutated *CEBPα* should not be over interpreted, given low numbers and missing information, whether or not *CEBPα* mutation was bi-allelic.[40]

In conclusion, our data allow for a reliable prognostic estimate of outcome in different, well defined molecular subgroups of patients with CN-AML after alloHSCT in CR1, with a remarkable impact of age and *FLT3*-ITD. Additional molecular features such as *FLT3*-ITD allelic burden or insertion site of *FLT3*-ITD,[11;41] as well as the simultaneous search for co-occurring and potentially interacting molecular markers might refine the accuracy of the estimate. The relevance of these additional characteristics should, however, be evaluated specifically in the setting of alloSCT, and in reliable numbers of patients. The study had not been designed to answer the question of whether or not patients with certain molecular subgroups should or should not undergo alloHSCT in CR1, nor can the findings be transferred to the entire patient population with newly diagnosed CN-AML. Nevertheless, the data might provide a basis for the decision between transplant and non-transplant consolidation strategies by giving a clear idea of the outcome to be expected after alloHSCT in a certain patient. In *FLT3*-ITD CN-AML, modifications of traditional transplant techniques did not improve outcome. Hence, studies evaluating the inclusion of innovative components, such as FLT3-inhibitors, are warranted.

Author Contributions:

Christoph Schmid, Myriam Labopin, Jordi Esteve, Aron Nagler and Mohamad Mohty designed the study, performed the analysis and interpreted and discussed the results.

Christoph Schmid wrote the manuscript, which was then refined by Myriam Labopin, Jordi Esteve, Aron Nagler and Mohamad Mohty

Emmanuelle Polge was the responsible data Manager

Myriam Labopin performed the statistical analysis

Gerard Socié, Etienne Daguindau, Liisa Volin, Anne Huynh, Jean Henri Bourhis, Noel Milpied, Jan Cornelissen, Patrice Chevallier, Johan Maertens, Pavel Jindra, Didier Blaise, Stig Lenhoff, and Norbert Ifrah contributed the largest numbers of patients, critically reviewed the manuscript and made substantial contribution to the Interpretation of the data and the the final text.

Frédéric Baron, Fabio Ciceri, Claude Gorin, Bipin Savani and Sebastian Giebel contributed to the design of the study, critically reviewed the manuscript and made substantial contribution to the interpretation of the data and the final text.

Conflict of Interest Disclosure

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Legend to tables

Table 1

Characteristics of *NPM1*/*FLT3*-ITD molecular subgroups among 702 patients undergoing allogeneic HSCT in first CR for AML with normal cytogenetics, as of molecular subgroups

Abbreviations: CR1, first complete remission; HSCT, hematopoietic stem cell transplantation; ATG, anti.thymocyte globulin; UD, unrelated donor; BuCy, Busulfan/Cyclophosphamide; BuFlu, Busulfan/Fludarabin; CyTBI, Cyclophosphamide/total body irradiation; FluMel, Fludarabin/Melphalan; GvHD, graft-versus-host disease; CyA, Ciclosporin A; MTX, Methotrexate; MMF, mycophenolate mofetil

*HLA identical sibling vs. unrelated donors

** different subgroups of unrelated donors (10/10, 9/10, 8/8 AG matched)

Table 2

Multivariate analysis of risk factors for 2-year outcome after allogeneic HSCT

Abbreviations: RIC, reduced intensity conditioning, MAC, myeloablative conditioning, MUD, matched unrelated donor, HLA, human leucocyte antigen, CR1, first complete remission HSCT, HSCT, hematopoietic stem cell transplantation

Table 3

Prognostic score for 2-year outcome following allogeneic HSCT in CN-AML. Presence of Flt3-ITD, age > median, and >1 course of chemotherapy to reach CR1 were included as risk factors.

Abbreviations: LFS, leukemia-free survival, SE, standard error, OS, overall survival CIR, cumulative incidence of relapse; NRM, non-relapse mortality

Table 1

		total	*NPM1*^{wt}/*FLT3*^{wt}	*NPM1*^{mut}/*FLT3*^{wt}	*NPM1*^{wt}/ *FLT3*-ITD	*NPM1*^{mut}/ *FLT3*-ITD	P
		n=702	n=290	n=68	n=75	n=269	
Age (years)	median (range)	51	52	52	47	51	0.05
		(18-71)	(21-70)	(24-67)	(19-70)	(18-71)	
Interval diagnosis to CR1 (days)	median (range)	43 (10-210)	47	38	48	39	<0.001
Interval CR1 to HSCT (days)	median (range)	106 (11-643)	110	107	98	104	0.5
Interval diag to HSCT (days)	median (range)	155 (55-714)	162	160	153	149	0.02
Year of HSCT	median	2010	2009	2009	2010	2010	<0.001
Patient sex	male	357	162	30	41	124	0.07
		51%	56%	44%	55%	46%	
	female	345	128	38	34	145	
		49%	44%	56%	45%	54%	
Donor sex	male	419	182	42	42	153	0.49
		60%	63%	63%	56%	57%	
	female	280	108	25	33	114	
		40%	37%	37%	44%	43%	
Female donor for male patient	no	577	235	58	58	226	0.33
		83%	81%	87%	77%	85%	
	yes	122	55	9	17	41	
		18%	19%	13%	23%	15%	
Donor type	HLA id sibling	383	163	38	38	144	0.82*
		55%	56%	56%	51%	54%	
	UD	319	127	30	37	125	
		45%	44%	44%	49%	47%	
	10/10 AG match	225	93	19	25	88	0.51**
	9/10 AG match	49	21	7	6	15	
	8/8 AG match	45	13	4	6	22	
Conditioning	myeloablative	330	116	31	43	140	0.007
		47%	40%	46%	57%	52%	
	BuCy	162	67	15	16	64	
	BuFlu	41	11	1	6	23	
	CyTBI	88	27	7	14	40	
	other	39	11	8	7	13	
	reduced	370	174	37	32	127	
		53%	60%	54%	43%	48%	
	BuFlu	192	90	16	13	73	
	FluMel	55	18	8	5	24	
	other	123	66	13	14	30	
CMV serostatus (donor/patient)	neg/neg	193	80	19	25	68	0.86
		28%	28%	29%	33%	25%	(0.6 for
	pos/neg	71	33	5	8	24	neg/neg
		10%	11%	8%	11%	9%	vs. other)
	neg/pos	170	67	14	16	72	
		24%	23%	21%	21%	27%	
	pos/pos	268	110	28	26	103	
		38%	38%	42%	35%	39%	
Stem cell source	BM	159	62	18	15	64	0.72
		23%	21%	27%	20%	24%	
	PB	543	228	50	60	205	
		77%	79%	74%	80%	76%	
Number of induction courses to reach CR1	1	486	200	47	35	204	<0.001
		75%	75%	73%	52%	81%	
	>=2	163	66	17	33	47	
		25%	25%	27%	49%	19%	

Total number of	1	83	38	11	8	26	0.27
chemotherapy		29%	29%	29%	28%	32%	
courses before HSCT	2	112	56	18	12	26	
		40%	42%	47%	41%	32%	
	3	62	33	4	5	20	
		22%	25%	11%	17%	24%	
	>3	25	6	5	4	10	
		9%	5%	13%	14%	12%	
Use of ATG	no	387	156	36	43	152	0.85
		55%	54%	53%	58%	57%	
	yes	312	133	32	31	116	
		45%	46%	47%	42%	43%	
HLA id sibling	no ATG	268	111	24	26	107	0.46
		71%	69%	63%	70%	75%	
	ATG	112	51	14	11	36	
		29%	31%	37%	30%	25%	
URD	no ATG	119	45	12	17	45	0.67
		37%	35%	40%	46%	36%	
	ATG	200	82	18	20	80	
		63%	65%	60%	54%	64%	
GVHD prophylaxis	CyA based	635	266	61	67	241	0.43
		91%	92%	90%	92%	90%	
	CyA+MTX	322	123	33	33	133	
	CyA+MMF	187	92	13	26	56	
	CyA+other	126	51	15	8	52	
	Tacrolimus based	37	16	2	4	15	
		5%	6%	3%	5%	6%	
	Tacrolimus+MMF	21	14	2	1	4	
	Tacrolimus+other	16	2	-	3	9	
	other	30	8	5	4	13	
		3%	2%	7%	3%	4%	
acute GVHD after	agvh<II	498	199	56	52	191	0.16
HSCT		74%	72%	85%	70%	73%	
	agvh>=II	180	78	10	22	70	
		27%	28%	15%	30%	27%	

Characteristics of *NPM1*/*FLT3*-ITD molecular subgroups among 702 patients undergoing allogeneic HSCT in first CR for AML with normal cytogenetics, as of molecular subgroups

Abbreviations: CR1, first complete remission; HSCT, hematopoietic stem cell transplantation; ATG, anti.thymocyte globulin; UD, unrelated donor; BuCy, Busulfan/Cyclophosphamide; BuFlu, Busulfan/Fludarabin; CyTBI, Cyclophosphamide/total body irradiation; FluMel, Fludarabin/Melphalan; GvHD, graft-versus-host disease; CyA, Ciclosporin A; MTX, Methotrexate; MMF, mycophenolate mofetil

*HLA identical sibling vs. unrelated donors

** different subgroups of unrelated donors (10/10, 9/10, 8/8 AG matched)

Table 2

		p	HR	95% CI	
				lower	upper
CIR	*FLT3*-ITD versus *FLT3*^{wt}	0.0003	2.23	1.44	3.46
	NPM1^{mut} versus NPM1^{wt}	0.47	0.85	0.56	1.31
	RIC vs MAC	0.032	1.25	0.81	1.93
	age > median	0.21	1.31	0.86	1.99
	UD vs HLA id	0.18	0.77	0.52	1.13
	Interval CR1 to HSCT >median	0.94	0.99	0.67	1.45
	Year of HSCT > median	0.32	0.81	0.54	1.22
	Nr of induction courses for CR1 >1	0.04	1.50	1.02	2.22
NRM	*FLT3*-ITD versus *FLT3*^{wt}	0.37	1.28	0.74	2.19
	NPM1^{mut} versus NPM1^{wt}	0.50	0.83	0.49	1.42
	RIC vs MAC	0.04	0.57	0.34	0.97
	age > median	0.00001	3.42	1.98	5.91
	UD vs HLA id	0.10	1.47	0.93	2.31
	Interval CR1 to HSCT >median	0.02	1.80	1.11	2.91
	Year of HSCT > median	0.41	0.81	0.48	1.35
	Nr of induction courses for CR1 >1	0.23	1.36	0.82	2.24
OS	*FLT3*-ITD versus *FLT3*^{wt}	0.001	1.85	1.29	2.66
	NPM1^{mut} versus NPM1^{wt}	0.24	0.81	0.57	1.15
	RIC vs MAC	0.53	0.89	0.62	1.28
	age > median	0.0000005	2.54	1.77	3.66
	UD vs HLA id	0.41	1.14	0.84	1.56
	Interval CR1 to HSCT >median	0.08	1.33	0.96	1.83
	Year of HSCT > median	0.41	0.86	0.60	1.23
	Nr of induction courses for CR1 >1	0.04	1.37	0.99	1.91
LFS	*FLT3*-ITD versus *FLT3*^{wt}	0.001	1.77	1.27	2.48
	NPM1^{mut} versus NPM1^{wt}	0.32	0.84	0.61	1.18
	RIC vs MAC	0.60	0.91	0.65	1.28
	age > median	0.0002	1.90	1.36	2.66
	UD vs HLA id	1.00	1.00	0.75	1.34
	Interval CR1 to HSCT >median	0.14	1.25	0.93	1.67
	Year of HSCT > median	0.23	0.82	0.60	1.13
	Nr of induction courses for CR1 >1	0.02	1.43	1.06	1.95

Multivariate analysis of risk factors for 2-year outcome after allogeneic HSCT

Abbreviations: RIC, reduced intensity conditioning, MAC, myeloablative conditioning, MUD, matched unrelated donor, HLA, human leucocyte antigen, CR1, first complete remission HSCT, HSCT, hematopoietic stem cell transplantation

Table 3

	Nr	LFS (%+/- SE)	OS (%+/- SE)	CIR (%+/- SE)	NRM (%+/- SE)
0 Factor	104	79+/-4	88+/-3	14+/-4	7+/-3
1 factor	322	73+/-3	77+/-2	15+/-2	12+/-2
2 or 3 factors	223	50+/-4	53+/-4	31+/-3	20+/-2
		0.002	0.003	0.0002	0.01

Prognostic score for 2-year outcome following allogeneic HSCT in CN-AML. Presence of Flt3-ITD, age > median, and >1 course of chemotherapy to reach CR1 were included as risk factors.

Abbreviations: LFS, leukemia-free survival, SE, standard error, OS, overall survival CIR, cumulative incidence of relapse; NRM, non-relapse mortality

Legend to figures

Figure 1.

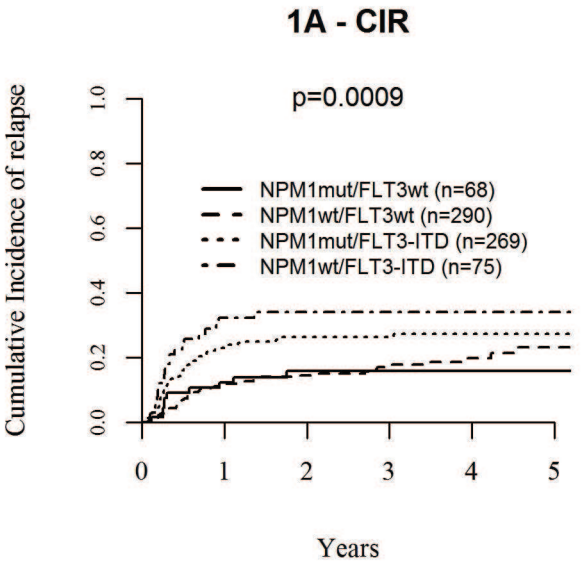
Cumulative incidence of relapse (CIR, A) and non-relapse mortality (NRM, B) after alloHSCT according to molecular subgroups

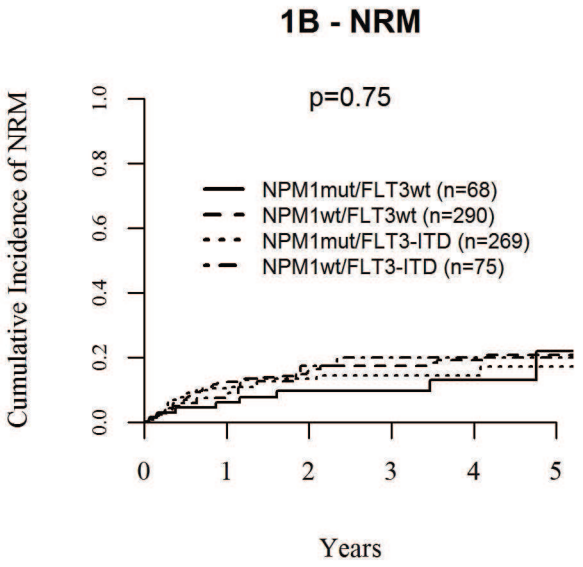
Figure 2.

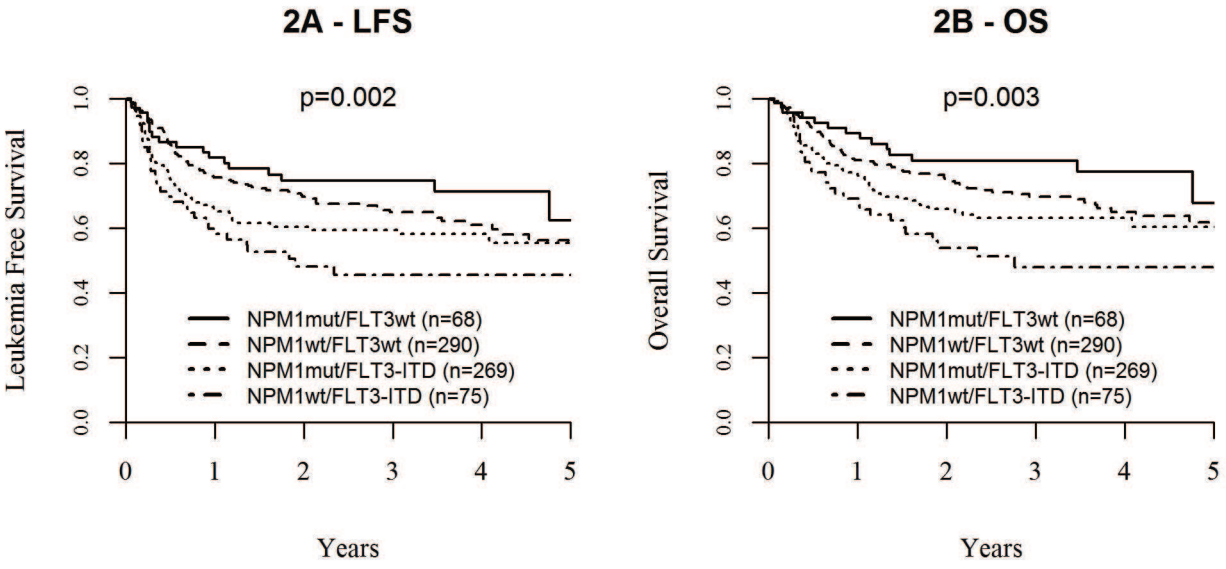
Leukemia free survival (LFS, A) and overall survival (OS, B) according to molecular subgroups

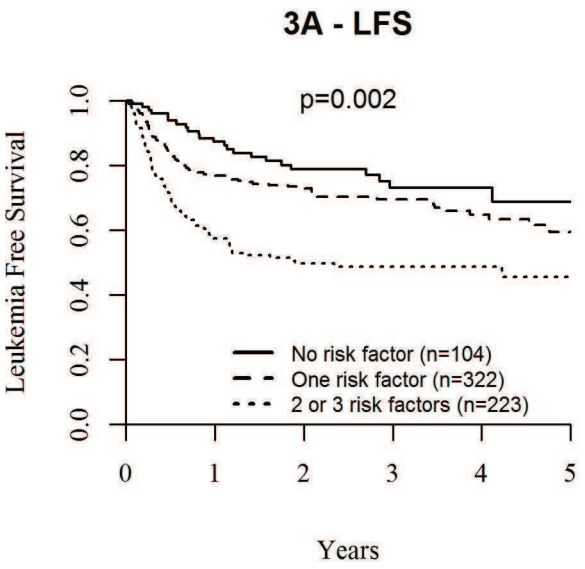
Figure 3.

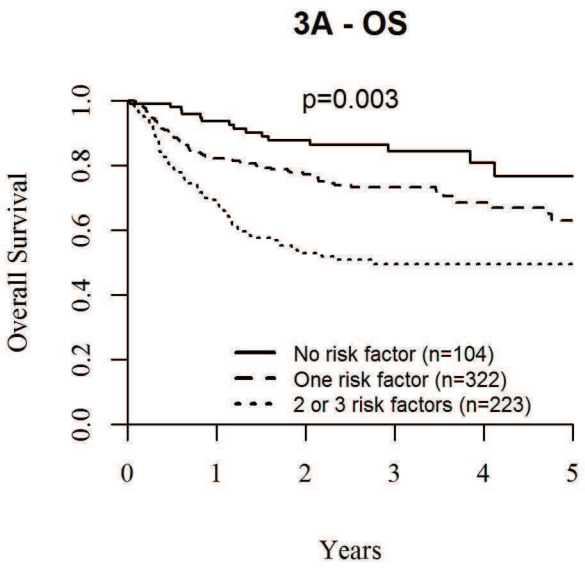
Estimate of leukemia free survival (LFS, A) overall survival (OS, B,), cumulative incidence if relapse (CIR, C,) and non-relapse mortality (NRM, D,) after allogeneic HSCT in CN-AML, based on independent prognostic parameters (FLT3-ITD, age, and the number of induction courses to achieve CR).

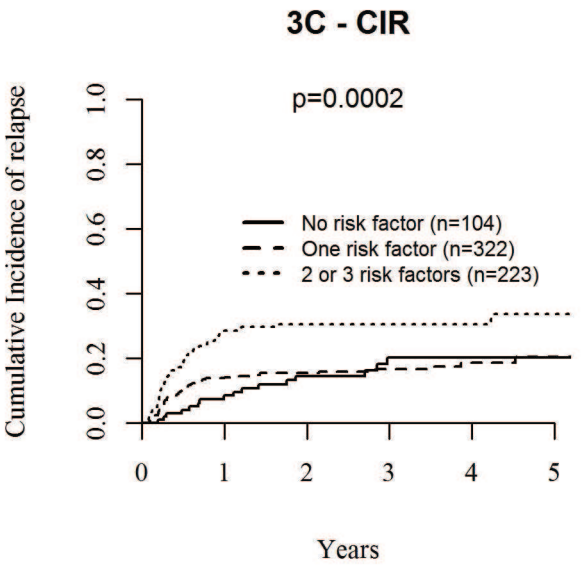

1A - CIR
p=0.0009
Cumulative Incidence of relapse
0.0
0.2
0.4
0.6
0.8
1.0
NPM1mut/FLT3wt (n=68)
NPM1wt/FLT3wt (n=290)
NPM1mut/FLT3-ITD (n=269)
NPM1wt/FLT3-ITD (n=75)
0
1
2
3
4
5
Years

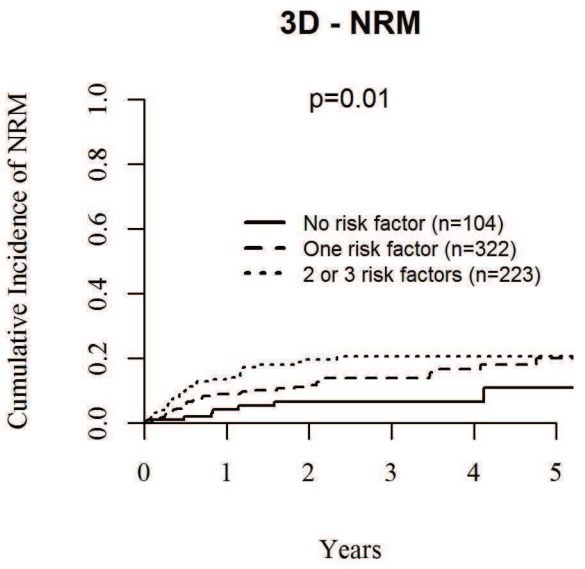

1B - NRM
p=0.75
Cumulative Incidence of NRM
0.0
0.2
0.4
0.6
0.8
1.0
NPM1mut/FLT3wt (n=68)
NPM1wt/FLT3wt (n=290)
NPM1mut/FLT3-ITD (n=269)
NPM1wt/FLT3-ITD (n=75)
0
1
2
3
4
5
Years


2A - LFS
p=0.002
Leukemia Free Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
NPM1mut/FLT3wt (n=68)
NPM1wt/FLT3wt (n=290)
NPM1mut/FLT3-ITD (n=269)
NPM1wt/FLT3-ITD (n=75)
2B - OS
p=0.003
Overall Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
NPM1mut/FLT3wt (n=68)
NPM1wt/FLT3wt (n=290)
NPM1mut/FLT3-ITD (n=269)
NPM1wt/FLT3-ITD (n=75)


3A - LFS
p=0.002
Leukemia Free Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
No risk factor (n=104)
One risk factor (n=322)
2 or 3 risk factors (n=223)


3A - OS
p=0.003
Overall Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
No risk factor (n=104)
One risk factor (n=322)
2 or 3 risk factors (n=223)


3C - CIR
p=0.0002
Cumulative Incidence of relapse
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
No risk factor (n=104)
One risk factor (n=322)
2 or 3 risk factors (n=223)


3D - NRM
p=0.01
Cumulative Incidence of NRM
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years
No risk factor (n=104)
One risk factor (n=322)
2 or 3 risk factors (n=223)

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Outcome and risk factor analysis of molecular subgroups in cytogenetically normal AML treated by allogeneic transplantation

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