The impact of concomitant cytogenetic abnormalities on acute myeloid leukemia with monosomy 7 or deletion 7q after HLA-matched allogeneic stem cell transplantation.

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Abstract

Monosomy 7 or deletion 7q (-7/7q-) is the most frequent adverse cytogenetic features reported in acute myeloid leukemia (AML) and is a common indication for allogeneic stem cell transplantation (SCT). Nevertheless, -7/7q- occurs frequently with other high-risk cytogenetic abnormalities such as complex karyotype (CK), monosomal karyotype (MK), monosomy 5 or deletion 5q (-5/5q-), 17p abnormalities (abn(17p)) or inversion of chromosome 3 (inv(3)), the presence of which may influence the outcomes after SCT.

A total of 1,109 patients has been allocated to this study. Two-year probability of leukemia-free survival (LFS) and overall survival (OS) were 30% and 36%, respectively. Two-year probability of non-relapse mortality (NRM) was 20%. We defined 5 different cytogenetic subgroups: the "-7/7q- ± CK group- designated group1", the "MK group-designated group 2", the "-5/5q- group- designated group 3", the 'abn(17p) group- designated group 4" and the "inv(3) group- designated group 5". The 2-year probability of LFS in first remission was 48% for group 1, 36.4% for group 2, 28.4% for group 3, 19.1% for group 4 and 17.3% for group 5,

respectively ($p<0.001$). Multivariate analysis confirmed those significant differences across groups.

SCT in -7/7q- AML provides durable response in one third of the patients. The presence of -7/7q- with or without CK in the absence of MK, abn(17p) or inv(3) is associated with a better survival after SCT. On the contrary, addition of MK, -5/5q-, abn(17p) or inv(3) identifies a sub-group of patients with poor prognosis even after SCT.

Introduction

Allogeneic stem cell transplantation (SCT) still remains the best consolidation strategy in patients with acute myeloid leukemia (AML) harbouring adverse cytogenetic features (1-5). These poor-risk cytogenetic events confer resistance to standard chemotherapy (6), and only a potent graft-versus-leukemia (GvL) effect arising from SCT may offer an opportunity of cure (7). The clinical benefit of SCT in high-risk AML has been well demonstrated (8-10). However, high-risk AML encompass a very heterogeneous group of disease categories including different cytogenetic abnormalities, mutational events or refractory disease (2, 11) and the benefit of SCT in each of these specific settings has been showed to be significantly different (12). Monosomy 7 or deletion 7q has been recognized for many years as a high-risk cytogenetic

feature in AML and it is the most frequent adverse abnormality reported (4). It is frequently associated with therapy-related AML, occurring after exposure to alkylating agents (13). It is also frequently co-occurring with other adverse cytogenetic features such as complex karyotype (CK), monosomy 5 or deletion 5q (-5/5q-) or inversion of chromosome 3 (inv(3)) (3). Consequently, it remains a very common indication for SCT and its specific outcome in that setting has never been thoroughly studied.

Monosomal karyotype (MK) has been associated with a very poor outcome with an estimated 4-year survival rate of 4% (14, 15). Within MK, the presence of monosomy 7 alone did not show any independent impact on survival (14, 16). However, in the transplant setting, a retrospective study from the EBMT addressing SCT for MK AML showed that monosomy 7 retained a significant impact on outcomes (17). We recently reported the outcome of 125 patients with AML and 17p abnormalities (abn(17p)) transplanted in first remission. Interestingly, the co-occurrence of -7 without -5/5q- translated into a much better survival than the frequent combination of -5/5q- and abn(17p) (18), which raises the questions of a potential better outcome after SCT for patients with -7/7q- and the influence of concomitant cytogenetic abnormalities. Subsequently, we studied a cohort of 501 patients with -5/5q- in which we were not able to demonstrate any impact of -7/7q- on outcomes after SCT (19). We therefore conducted a retrospective study focusing on patients with AML with -7/7q- undergoing SCT and we analyzed the impact of frequent co-occurring cytogenetic abnormalities such as CK, MK, -5/5q-, abn(17p) and inv(3)/t(3;3).

Methods

Patient selection and data collection

This is a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a non-profit, scientific society representing more than 600 transplant centers mainly in Europe that are required to report all consecutive stem cell transplantations and their follow-up once a year. Data are entered, managed and maintained in a central database with internet access; each EBMT center is represented in this database. Audits are routinely performed to determine the accuracy of the data. Patients or legal guardian provide informed consent authorizing the use of their personal information for research purposes. The study was approved by the ALWP review board.

Eligibility criteria for the study included all patients $\geq$ 18 years and with de novo or secondary AML transplanted between 1 January 2000 and 31 December 2016 from an HLA-matched sibling (MSD) or a fully-matched (10/10) unrelated donor (MUD). Patients undergoing second transplantation as well as patients having a haplo-identical or cord-blood transplantation were excluded. We further selected patients harboring -7/7q- and having a full karyotype report within the database in order to study the prognostic impact of additional cytogenetic features. A total of 1,109 patients from 179 centers met the study inclusion criteria and were selected for further analysis. Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gy, a total dose of oral busulfan (Bu) greater than 8 mg/kg, or a total dose of intravenous Bu greater than 6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) (20).

The following variables were selected and included in the analysis: year of transplantation, age, gender, white blood cell count (WBC) at diagnosis, de novo or secondary AML condition,

number of induction courses to achieve CR, status at transplantation, time from diagnosis to SCT, type of conditioning regimen, use of TBI, in vivo T-cell depletion (including both anti-thymocyte globulins and alemtuzumab), cytomegalovirus (CMV) status of donor and recipient, donor type, source of stem cells, Karnofsky performance status at transplantation, engraftment, presence of acute and chronic graft-versus-host disease (GvHD), grade of acute GvHD, severity of chronic GVHD. Secondary AML has been defined by AML with previous diagnosis of myelodysplastic syndromes or myeloproliferative neoplasms or AML secondary to cytotoxic therapies. For the analysis of additional cytogenetic abnormalities, we included in our analysis the presence of abnormalities of 3q26 (e.g., inv(3)(q21q26) or t(3;3)(q21;q26)), abnormalities leading to loss of chromosome 17p (abn(17p)), monosomy 5 or deletion 5q, monosomal karyotype (MK) and complex karyotype (CK) classified according to the cytogenetic status by Medical Research Council UK criteria (3).

Statistical analysis and endpoints definitions

Primary endpoint was LFS. Secondary endpoints included relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), acute and chronic GvHD, and refined GvHD-free/relapse-free survival (GRFS). All outcomes were measured from the time of transplant. LFS was defined as survival without relapse; patients alive without relapse were censored at the time of last contact. OS was based on death from any cause. NRM was defined as death without previous relapse. GRFS was defined as survival without grade 3-4 acute GvHD, extensive chronic GvHD, relapse or death(21). Surviving patients were censored at the time of last contact. The probabilities of OS, LFS, and GRFS were calculated by the Kaplan-Meier test,

and those of acute and chronic GVHD, NRM, and relapse by 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 and relapse were the competing risks.

For all univariate analyses, continuous variables were categorized and the median value was used as a cut-off point. A Cox proportional hazards model was used for multivariate regression including factors associated with LFS in univariate analysis and individual cytogenetics abnormalities. Finally, we defined five groups according to the complexity of the karyotype, the presence of a MK and the presence or not of individual cytogenetic abnormalities significantly associated with the outcome. Patient, disease and transplant-related characteristics for the five groups were compared by using χ^2 statistics for categorical variables and the Kruskall-Wallis test for continuous variables. Factors differing in distribution between the groups or conceptually important were included in the final Cox model. Proportional hazards assumptions were checked systematically using the Grambsch-Therneau residual-based test. All interactions between cytogenetics groups and other covariates were tested. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R 3.4.1 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results

Patients' characteristics

Table 1 summarize patients' characteristics of the entire population as well as separately for those harbouring 7q- or -7. A total of 1,109 patients met the inclusion criteria and were included in the present analysis. Median follow-up using the reverse Kaplan-Meier was 59 months (inter-quartile range, 26-106). Median age at SCT was 52 years (range, 18-76). The main MAC regimens were the combination of cyclophosphamide with TBI (33%) or cyclophosphamide with busulfan (32%), and the two most frequent RIC regimens were fludarabine and busulfan (32%) followed by fludarabine and low dose TBI (18%). For GvHD prophylaxis, patients mostly received the combination of cyclosporine with methotrexate (42%) or cyclosporine with mycophenolate mofetil (27%). As to cytogenetics, karyotype from 468 patients (52%) did not contain additional studied cytogenetic abnormalities, whereas 532 (48%) and 425 (38%) patients fulfilled criteria for MK and CK AML, respectively, in addition to -7/7q-. Both categories presented a great overlap, with 338 patients meeting characteristics of both MK and CK. The presence of -5/5q- was seen in 240 patients (22%), while abn(17p) and inv(3) were present in 128 (12%) and 111 (10%) patients, respectively. When looking separately to patients with 7q- or -7, we observed significantly more MK and inv(3) in -7 patients. All these cytogenetic categories presented a great overlap, as illustrated in Figure 1.

Transplantation outcome by univariate analysis: relapse incidence, non-relapse mortality, leukemia-free survival, overall survival, cause of death, and graft-versus-host disease in the entire cohort.

The 2-year cumulative incidence of relapse in the overall series was 49.7% [95% CI: 46.6-52.7] (see supplemental Figure 1A). In univariate analysis, RI was significantly associated with

disease status, being higher for patients transplanted in subsequent remission and those with active disease at the time SCT. Transplant from MSD was also followed by higher RI than SCT from MUD. Age, secondary AML, performance status, stem cell source, conditioning intensity and in vivo TCD were not associated with RI. All additional cytogenetic abnormalities tested were significantly associated with increased RI as detailed in Table 2.

The 2-year probability of NRM was 20.1% [95% CI: 17.7-22.6] (see supplemental Figure 1B). The variables significantly associated with reduced NRM were SCT from MSD, younger donor's age, being in CR1 at the time of SCT, de novo AML compared to secondary AML and a better performance status at the time of SCT. All other variables, including additional cytogenetic abnormalities were not associated with mortality as shown in Table 2 for additional cytogenetic abnormalities.

The overall 2-year probability of LFS was 30.2% [95% CI: 27.3-33] (see supplemental Figure 1C). In univariate analysis, we found a significant better LFS with the following variables; SCT performed after 2009, being in CR1 at the time of SCT versus subsequent disease status, de novo AML compared to secondary AML and a better performance status at the time of SCT. In contrast, donor type, age, stem cell source and conditioning intensity did not have any impact on LFS. Finally, every studied additional cytogenetic abnormality was associated with worse LFS as detailed in Table 2.

Two-year OS was 36.4% [95% CI: 33.4-39.4] (see supplemental Figure 1D). In univariate analysis, a worse OS was observed in patients transplanted in subsequent disease status compared to CR1, with secondary AML, with a worse KPS and among those male recipients having a female donor. In contrast, age, donor type, year of SCT, stem cell source and conditioning intensity did not have an impact on OS. As for LFS, additional cytogenetic adverse features were all associated with decreased OS as shown in Table 2. The main causes of death were disease-related followed by infections and GvHD.

The 100-day cumulative incidence of grade II-IV and III-IV acute GvHD was 30.7% [95% CI: 27.9-33.5] and 11.3% [95% CI: 9.5-13.3], respectively. The 2-year cumulative incidence of total and extensive chronic GvHD was 30.9% [95% CI: 28-33.8] and 15.8% [95% CI: 13.6-18.2], respectively. The 2-year probability of GRFS was 20.8% [95% CI: 18.3-23.3]. A higher cumulative incidence of grade II-IV acute GvHD was associated with MUD, younger age, active disease at the time of SCT and patient's CMV negativity. In addition, the presence of CK was associated with lower incidence of acute GvHD (26.4% [95% CI: 22.2-30.8] as compared to 33.3% [95% CI: 29.7-37] in patients without CK, p=0.03). A lower incidence of chronic GvHD was associated with active disease at the time of SCT. Regarding additional adverse cytogenetic features, presence of MK, abn(17p) and inv(3) were all associated with less chronic GvHD. In vivo TCD was associated with a reduced incidence of extensive chronic GvHD. A significant better GRFS was observed among patients transplanted after 2009, patients in CR1, with de novo AML compared to secondary AML and among those with better KPS at the time of SCT. A female donor to male recipient translated also into worse GRFS.

Additionally, in vivo TCD was significantly associated with better GRFS. Finally, all studied additional cytogenetic abnormalities correlated significantly with worse GRFS as detailed in Table 2.

Prognostic factors by multivariate analysis in the entire population.

Active disease at the time of SCT remained the strongest predictive factor for worse RI, NRM, LFS, OS and GRFS in multivariate analysis as shown in Table 3. Subsequent remissions were associated with a decreased LFS, OS and GRFS, and with an increased NRM. Of note, age lost any significant impact on outcomes in our multivariate model. A better performance status correlated strongly with better LFS, OS and GRFS due to significantly lower NRM. Secondary AML was also associated with worse LFS, OS and GRFS, as well as with increased NRM, but had no impact on RI. The use of MUD correlated with higher NRM, which did not translate into worse LFS and OS. Use of RIC regimens was associated with worse LFS than MAC regimens. CMV status of the donor and/or the recipient lost any impact in multivariate analysis. As for additional adverse cytogenetic abnormalities, none of them impacted NRM in our Cox model. CK was not significantly associated with RI, LFS, OS and GRFS while MK showed a significantly increased RI and decreased LFS and GRFS. -5/5q-, abn(17p) and inv(3) were all associated with increased RI and worse LFS, OS and GRFS.

Outcomes by cytogenetic subgroups.

In order to elucidate the impact of additional cytogenetic abnormalities on outcomes of patients with AML and -7/7q- after transplantation, we defined 5 different subgroups within our entire cohort in a hierarchical manner. Due to the overlap between all additional cytogenetic abnormalities, our hierarchy was based on the statistical weight of CK, MK, -5/5q-, abn(17p) and inv(3) resulting from our previous multivariate analysis, and on their capability to distinguish biologically and clinically meaningful cytogenetic categories. The "-7/7q- ± CK group" included 523 -7/7q- patients with or without CK but in the absence of MK, -5/5q, abn(17p) or inv(3). The "MK group" contained 199 patients fulfilling the definition of MK in the absence of -5/5q-, abn(17p) or inv(3). The "-5/5q- group" comprised 151 -7/7q- patients in combination with -5/5q- with the exception of abn(17p) and inv(3). In the "abn(17p) group", 125 patients harbored abn(17p) in addition to -7/7q- excluding 3 patients with inv(3). Finally, the "inv(3) group" encompassed 111 patients to the combination of -7/7q- with inv(3) regardless of the presence of other adverse cytogenetic features. As shown in the supplemental material, there were a few differences in baseline characteristics between those 5 groups. Patients in the "inv(3) group" were younger and more frequently transplanted with active disease. When we included those 5 groups into a Cox model, we found that the "MK", "-5/5q-", "abn(17p)" and "inv(3)" groups were all associated with a significant higher RI and decreased LFS and OS compared to both the "7q- and -7 ± CK" groups as shown in Table 4.

As disease status at the time of SCT is a strong and well-established prognostic factor of outcomes after SCT, we subsequently decided to focus on the 702 patients transplanted in CR1 as illustrated in Figure 2. The 2-year cumulative incidence of relapse was 36.7% for the "-7/7q-

± CK group", 47.8% for the "MK group", 51% for the "-5/5q- group", 62.9% and 68.4% for the "inv(3) group" ($p<0.0001$, Figure 2A), which translated into a 2-year probability of LFS of 48%, 36.4%, 28.4%, 19.1% and 17.3% for the "-7/7q- ± CK", "MK", "-5/5q-", "abn(17p)" and "inv(3)" groups, respectively ($p<0.0001$, Figure 2C). The 2-year NRM was similar across our 5 cytogenetic groups ($p=0.69$, Figure 2B) but the 2-year probability of OS was significantly influenced by subgroups, being 58.2%, 44.6%, 36%, 18.7% and 21.8% for the "-7/7q- ± CK", "MK", "-5/5q-", "abn(17p)" and "inv(3)" groups, respectively ($p<0.0001$, Figure 2D). The 2-year probabilities of GRFS were 36.6% [95% CI: 31.1-42.1] for the "-7/7q- ± CK" group, 20.8% [95% CI: 13-28.5] for the "MK" group, 17.2% [95% CI: 9.2-25.2] for the "-5/5q-" group, 7.3% [95% CI: 1.5-13.2] for the "abn(17p)" group and 13.1% [95% CI: 3.4-22.8] for the "inv(3)" group ($p<0.0001$). When studying separately deletion 7q from monosomy 7 within the "-7/7q- ± CK group", we found in multivariate analysis than monosomy 7 showed a significant increase in RI , which translated into worse LFS, without impacting OS or GRFS (Table 4 and see supplemental Figure 2).

Discussion

-7/7q- is the most frequent autosomal monosomy reported in AML (22, 23) and is consistently associated with a very bad prognosis after chemotherapy alone (3, 24). As other high-risk AML, SCT appears as the best consolidation strategy with prolonged disease-free survival in about 40% of the patients (1, 8, 9, 25). However, we obtained 2-year LFS and OS of 30% and 36%, respectively in our large cohort, which remains worse than the expected survival for high-risk AML after SCT (9). Patients transplanted in CR1 could enjoyed a better 2-year LFS of 37%. The poorer results observed in our population could either be explained by -7/7q- which remains a well-known adverse feature in AML, or by other bad risk factors included in this cohort. We found the usual prognostic factors associated with worse outcomes such as active disease at SCT (8) and bad performance status (26). We also found that sAML was significantly associated with increased NRM and decreased OS as previously described (27, 28), mainly due to the excess of toxicity from previous chemotherapy found in therapy-related AML. In contrast, we did not find any impact of age in multivariate analysis (1, 29). Finally, a RIC

regimen was associated with worse LFS without impacting OS, despite the chemo-refractory properties of AML with MK and/or TP53 dysfunction included in this cohort (30, 31).

-7/7q- is the most frequent cytogenetic feature reported as sole abnormality (23), which is well illustrated within our population with 42% of the patients harboring -7/7q- without CK, MK, -5/5q-, abn(17p) and inv(3). As suggested by our previous dataset (18), we hypothesized that the prognosis of our cohort would be dictated by the presence of additional adverse cytogenetic abnormalities. While CK did no show an impact on outcomes in multivariate analysis, we found a significant worse survival in patients harboring MK, -5/5q-, abn(17p) and inv(3). As illustrated by our Venn diagram, most of those abnormalities are combined with each other, making it difficult to avoid the confounding effect of overlapping cytogenetic categories. We therefore decided to define 5 different groups based on a hierarchical prognostic effect of MK, -5/5q-, abn(17p) and inv(3). This cytogenetic stratification allowed us to confirm the strong negative impact of MK, -5/5q-, abn(17p) and inv(3). Patients harboring -7/7q- in combination or not with additional cytogenetic abnormalities with the exception of MK, -5/5q-, abn(17p) and inv(3) showed a 2-year probability of LFS of 48% if transplanted in CR1, better than the expected survival after SCT in high-risk AML (9). The “MK” and “-5/5q-” groups both showed a significantly decreased survival compared to the “-7/7q- ± CK” group. Outcomes for the “-5/5q-” group appeared somehow worse than for “MK” group. Similarly, Middeke et al. showed in a smaller cohort that -5/5q- led to worse outcome than MK after SCT, but in contrast to their observations (32), we still found a negative impact of MK on outcomes after SCT as shown by others (17, 33-35). We may speculate that the worse results observed with -5/5q- might be

related to the higher prevalence of *TP53* mutations in this entity (36, 37), but we cannot further analyze this hypothesis in the context of a registry-based study. One of the most important limitations of our study is the lack of molecular data within the registry, which are now routinely available. Our hierarchical stratification may indeed reflect the increasing frequency of *TP53* mutations across the groups as previously observed (38, 39). Our "abn(17p)" group translated into a 2-year probability of LFS of only 19% if transplanted in CR1, which is worse than previously published data (18, 40). These worse results might be related to the presence of 66% -5/5q- within the "abn(17p)" group, which supports our previous observation of the deleterious effect of the combination of -5/5q- and abn(17p) on outcomes after SCT (18). To further support the negative combinatorial impact of -5/5q- and abn(17p), we subsequently studied separately -5/5q-, abn(17p) and the combination of -5/5q- with abn(17p). We confirmed that -5/5q- with abn(17p) led to worse survival than each abnormality on its own (data not shown). Regarding inv(3), we showed a 2-year LFS of 17% in patients transplanted in CR1. Our survival appears inferior to the 2-year LFS of 24% reported recently by Halaburda et al (41). -7/7q- is the most frequent additional cytogenetic abnormality found in inv(3) AML (41-44). A negative impact of the combination of inv(3) and -7/7q- has been suggested in univariate analysis in previous reports, but not confirmed in multivariate analysis (41, 44). However, one or more haploinsufficient tumor suppressor genes on the long arm of chromosome 7, such as CUX1, may cooperate with inv(3) to lead to a highly refractory AML clone (45, 46). Our observations support this additive effect of -7/7q- and inv(3) on outcomes after SCT. Finally, a better prognosis for 7q- than -7 has been suggested in several studies, mainly performed in patients with MDS (47, 48), while others did not show significant differences in survival (49, 50). Our

observations support some different impacts from both -7 and 7q-, which remained significant in multivariate analysis only with regard to the relapse incidence.

Our cohort included the most frequent adverse cytogenetic features reported in AML and we have clearly shown that they are not equal in terms of the expected benefit from SCT. If -7/7q- AML with or without CK demonstrated significant improved survival after SCT, the benefit of SCT is much more limited with the addition of MK, -5/5q-, abn(17p) and inv(3). Patients harboring MK, -5/5q- and abn(17p) have a high frequency of *TP53* mutations (36-38, 51, 52), which is known to be associated with chemo-resistance and lower sensitivity to a graft-versus-leukemia effect (18). The first goal in those high-risk patients is to bring them into remission (39) with TP53-independent drugs such as decitabine (53) or venetoclax (54, 55). However, even if transplanted in CR1, the benefit of SCT remains questionable, especially in those harboring the combination of -5/5q- with abn(17p) or the presence of inv(3). The very short median time to relapse after SCT forces us to integrate early post-transplant interventions such as hypomethylating agents (56-58), prophylactic donor leukocyte infusions (59, 60) or combination of both. Another limitation of our study is the lack of information about post-SCT interventions within the registry. However, such strategies should be further studied, especially in specific cytogenetic subgroups such as the combination of -5/5q- with abn(17p). Patients harboring -7/7q- alone or in combination with inv(3) show frequent association with *RAS* pathway mutations (22, 42, 45), which could be targeted by small molecule inhibitors (61, 62). However, the best strategy to handle those very high-risk AML after SCT is still to be

discovered and efforts have to be made in the next future to study novel therapeutic interventions with or without SCT.

In conclusions, we have reported a very large population of 1109 AML with -7/7q- after SCT, including the most common adverse cytogenetic features such as CK, MK, -5/5q-, abn(17p) and inv(3). A transplant strategy in our cohort led to a 2-year survival in about 30% of the patients. One of the largest limitations in this study might be the lack of centralized cytogenetic analysis and the selection of patients with an available full cytogenetic report, an essential requirement for the proposed analysis. Active disease at the time of SCT remains the strongest prognostic factor of worse survival and cautions have to be made when bringing those patients to SCT. Novel therapeutic pre-transplant strategies must be developed to increase the proportion of patients into remission before SCT. The main finding of our study is that the benefit of SCT remains highly dependent on the presence of other adverse features such as MK, -5/5q-, abn(17p) and inv(3). The benefit of SCT appears debatable particularly in patients harboring abn(17p) and inv(3) with the current standard approach, especially if not in CR1 at the time of SCT. The decision of SCT for those patients should be integrate with the development of pre-transplant and post-transplant pharmacological and immunological maneuvers to sustain response. Early withdrawal of immunosuppression, maintenance therapy and DLI should be considered but inclusion in clinical trials may help us to better define the best strategies in the future.

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Figures' legend

Figure 1: Additional cytogenetic abnormalities.

A total of 468 patients harboured -7/7q- without additional adverse cytogenetic features. The vast majority of patients showed MK (48%) or CK (38%) in combination with -7/7q-. The presence of -5/5q- was seen in 240 patients (22%), while abn(17p) and inv(3) were present in 128 (12%) and 111 (10%) patients, respectively. The Venn diagram illustrates well that most of those adverse cytogenetic features were not present as a single additional abnormality but rather exist in combination.

Figure 2: Relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS) and overall survival (OS) by cytogenetic groups in patients transplanted in first remission.

The 2-year cumulative incidence of relapse was 36.7% [95% CI: 31.3-42.2] for the "-7/7q- ± CK group", 47.8% [95% CI: 38.3-56.7] for the "MK group", 51% [95% CI: 40.1-60.9] for the "-5/5q- group", 62.9% [95% CI: 51.3-72.4] and 68.4% [95% CI: 52.7-79.8] for the "inv(3) group" ($p<0.0001$) (A) and the 2-year probability of NRM was similar across the 5 groups, reaching 16.4% [95% CI: 13.6-19.3] ($p=0.69$) (B). The 2-year probability of LFS was 48% [95% CI: 42.3-53.6], 36.4% [95% CI: 27.5-45.4], 28.4% [95% CI: 18.9-37.9], 19.1% [95% CI: 10.4-27.8] and 17.3% [95% CI: 6.5-28.1] for each group, respectively ($p<0.0001$) (C). The 2-year probability OS was 58.2% [95% CI: 52.6-63.9] for the "-7/7q- ± CK group", 44.6% [95% CI: 35.2-53.9] for the "MK group", 36% [95% CI: 25.8-46.3] for the "-5/5q- group", 18.7% [95% CI: 9.9-27.4] for the "abn(17p) group" and 21.8% [95% CI: 9.8-33.8] for the "inv(3) group" ($p<0.0001$) (D).

Table 1
Patients' characteristics

	Entire population	7q-	-7	p-value
N	1109	331	778	
Median follow-up (inter-quartile range)	59 months (26-106)	56 months (25-102)	59 months (26-108)	0.45
Median age, years (range)	52 (18-76)	51.9 (18.1-70.8)	52.2 (18-76.1)	0.46
Time from diagnosis to SCT, months (range)	4.9 (0.4-387)	5.1 (1.5-386.8)	4.8 (0.4-280.8)	0.04
Median year of SCT (range)	2009 (2000-2015)	2009 (2000-2015)	2009 (2000-2015)	0.45
Disease status at SCT, N (%) CR1 CR2/CR3 Active disease	 702 (63) 58 (5) 348 (32)	 222 (67) 18 (5) 91 (28)	 480 (62) 40 (5) 258 (33)	0.18
Secondary AML, N (%)	213 (19)	62 (19)	151 (19)	0.79
Donor type, N (%) MSD/MUD	496/613 (45/55)	164/167 (49/50)	332/446 (43/57)	0.04
Patients' gender, N (%) M/F	597/511 (54/46)	168/163 (51/49)	332/446 (43/57)	0.17
Female donor to male recipient, N (%)	184 (17)	54 (17)	130 (17)	0.89
KPS ≥ 80%, N (%)	966 (93)	297 (96)	669 (92)	0.04
Patient CMV positive, N (%)	685 (64)	215 (67)	470 (62)	0.11
Donor CMV positive, N (%)	523 (49)	155 (49)	368 (49)	0.95
Conditioning intensity, N (%) MAC/RIC	549/560 (49/51)	170/161 (51/49)	379/399 (49/51)	0.42
Stem cell source, N (%) BM/PB	165/944 (15/85)	61/270 (18/82)	104/674 (13/87)	0.03
In vivo TCD, N (%)	625 (56)	185 (56)	440 (57)	0.84
CK, N (%)	425 (38)	135 (41)	290 (37)	0.27
MK, N (%)	532 (48)	70 (21)	462 (59)	0.001
-5/5q-, N (%)	240 (22)	78 (24)	162 (21)	0.31
abn(17p), N (%)	128 (12)	36 (11)	92 (12)	0.65
inv(3), N (%)	111 (10)	10 (3)	101 (13)	0.001

Abbreviations: SCT: allogeneic stem cell transplantation; N: number; CR1: first remission; CR2: second remission; CR3: third remission; AML: acute myeloid leukemia; MSD: matched sibling donor; MUD: matched unrelated donor; M: male; F: female; KPS: Karnofsky's performance status; CMV: cytomegalovirus; MAC: myeloablative conditioning regimen; RIC: reduced-intensity conditioning regimen; BM: bone marrow; PB: peripheral blood; TCD: T-cell depletion; CK: complex karyotype; MK: monosomal karyotype; -5/5q-monosomy 5 or deletion 5q; abn(17p): 17p abnormalities; inv(3): inversion of chromosome 3.

Table 2
Univariate analysis of additional cytogenetic abnormalities

	RI		NRM		LFS		OS		GRFS		Grade II-IV aGVHD		cGvHD	
	2y (%, 95%CI)	p	2y (%, 95%CI)	p	2y (%, 95%CI)	p	2y (%, 95%CI)	p	2y (%, 95%CI)	p	2y (%, 95%CI)	p	2y (%, 95%CI)	p
CK														
Yes	57 (52-62)	<0.0001	20 (16-24)	0.99	23 (18-27)	<0.0001	27 (22-31)	<0.0001	13 (10-16)	<0.0001	26 (22-31)	0.03	29 (25-34)	0.44
No	45 (41-49)		20 (17-23)		35 (31-39)		42 (38-46)		27 (22-29)		33 (30-37)		32 (28-36)	
MK														
Yes	60 (55-64)	<0.0001	19 (15-22)	0.27	22 (18-26)	<0.0001	27 (23-31)	<0.0001	13 (10-16)	<0.0001	32 (28-36)	0.4	28 (24-32)	0.05
No	41 (37-45)		22 (18-25)		38 (34-42)		45 (41-50)		28 (24-32)		30 (26-34)		34 (30-38)	
Abn(5q)														
Yes	61 (54-67)	<0.0001	20 (15-26)	0.95	19 (14-25)	<0.0001	23 (17-28)	<0.0001	12 (8-16)	<0.0001	29 (23-35)	0.5	29 (23-35)	0.43
No	47 (43-50)		20 (17-23)		33 (30-37)		40 (37-44)		23 (20-26)		31 (28-34)		32 (28-35)	
Inv(3)														
Yes	70 (60-77)	<0.0001	17 (10-25)	0.39	14 (7-20)	<0.0001	20 (12-28)	<0.0001	9 (3-15)	0.0002	37 (28-46)	0.15	20 (12-28)	0.04
No	48 (44-51)		21 (18-23)		32 (29-35)		38 (35-42)		22 (19-25)		30 (27-33)		32 (29-35)	
Abn(17p)														
Yes	62 (45-51)	<0.0001	22 (15-30)	0.57	16 (9-23)	<0.0001	16 (8-22)	0.002	8 (3-13)	<0.0001	32 (24-41)	0.6	23 (16-31)	0.03
No	48 (53-64)		20 (17-23)		32 (29-35)		39 (36-42)		23 (20-25)		31 (28-34)		32 (29-35)	
7q- vs -7														
7q-	44 (38-49)	0.005	21 (17-26)	0.72	35 (30-41)	0.004	42 (36-47)	0.015	26 (21-31)	0.002	28 (23-33)	0.16	32 (26-37)	0.65
-7	52 (49-56)		20 (17-23)		28 (25-32)		34 (31-38)		19 (16-22)		32 (29-35)		31 (27-34)	

Abbreviations: CK: complex karyotype; MK: monosomal karyotype; Abn(5q): monosomy 5 or deletion 5q; Inv(3): abnormalities of 3q26 (inv(3)/t(3;3); abn(17p): 17p abnormalities; 7q-: deletion 7q; -7: monosomy 7; RI: relapse incidence; 2y: 2 years; CI: confidence interval; p: p-value; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; GRFS: graft-versus-host disease and relapse-free survival; aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host-disease.

Table 3

Multivariate analysis using a Cox proportional hazard model in the entire cohort for RI, NRM, OS and LFS. Only variables with a p<0.05 in univariate analysis were included in this analysis

	RI			NRM			LFS			OS			GRFS		
	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI
Age (per 10 year)	0.48	0.97	0.9-1.05	0.5	1.04	0.92-1.18	0.73	0.99	0.92-1.06	0.79	1.01	0.94-1.08	0.86	0.99	0.93-1.06
MUD vs MSD	0.08	0.83	0.67-1.02	0.005	1.6	1.15-2.21	0.86	1.02	0.85-1.21	0.33	1.09	0.91-1.31	0.91	0.99	0.84-1.17
Year of SCT	0.19	0.99	0.96-1.01	0.089	0.97	0.94-1.01	0.05	0.98	0.96-1.00	0.09	0.98	0.96-1.00	0.054	0.98	0.97-1.00
Secondary AML vs de novo	0.73	0.96	0.76-1.21	0.00006	1.86	1.37-2.52	0.05	1.2	1.00-1.44	0.01	1.28	1.06-1.54	0.048	1.20	1.00-1.43
CR2/3 vs CR1	0.6	1.14	0.71-1.82	0.0004	2.39	1.47-3.89	0.009	1.56	1.12-2.18	0.008	1.60	1.13-2.27	0.027	1.45	1.04-2.01
Active disease vs CR1	<0.00001	1.69	1.39-2.06	0.0057	1.53	1.13-2.06	<0.00001	1.64	1.39-1.93	<0.00001	1.63	1.38-1.93	<0.00001	1.51	1.29-1.77
KPS≥80%	0.47	0.87	0.59-1.27	0.00001	0.37	0.24-0.56	0.001	0.62	0.47-0.83	0.00007	0.55	0.42-0.74	0.002	0.65	0.49-0.86
RIC vs MAC	0.2	1.14	0.93-1.39	0.17	1.24	0.91-1.68	0.04	1.19	1.01-1.4	0.1	1.15	0.97-1.36	0.06	1.17	0.99-1.37
Female to Male	0.93	0.99	0.78-1.26	0.13	1.31	0.93-1.85	0.45	1.08	0.89-1.31	0.33	1.11	0.9-1.35	0.16	1.14	0.95-1.38
In vivo TCD	0.94	1.01	0.82-1.24	0.15	0.8	0.58-1.09	0.4	0.93	0.78-1.11	0.32	0.91	0.76-1.09	0.007	0.80	0.68-0.94
Patient CMV+	0.35	0.91	0.75-1.11	0.84	1.03	0.76-1.4	0.5	0.95	0.8-1.11	0.48	0.94	0.79-1.12	0.19	0.9	0.77-1.05
Donor CMV+	0.5	1.07	0.88-1.29	0.86	0.97	0.73-1.31	0.64	1.04	0.89-1.22	0.46	1.07	0.9-1.13	0.71	0.97	0.83-1.13
CK	0.93	1.01	0.8-1.27	0.19	1.26	0.89-1.78	0.38	1.09	0.9-1.32	0.07	1.2	0.98-1.46	0.098	1.17	0.97-1.41
MK	0.007	1.39	1.1-1.77	0.85	0.97	0.67-1.39	0.04	1.24	1.01-1.51	0.08	1.2	0.98-1.48	0.01	1.27	1.05-1.55
-5/5q-	0.009	1.4	1.09-1.80	0.85	1.04	0.69-1.57	0.02	1.28	1.03-1.59	0.019	1.3	1.05-1.62	0.33	1.11	0.90-1.37
abn(17p)	0.003	1.55	1.16-2.07	0.35	1.27	0.77-2.07	0.003	1.46	1.14-1.87	0.007	1.4	1.11-1.85	0.016	1.35	1.06-1.73
Inv(3)	0.0003	1.78	1.3-2.42	0.73	1.11	0.63-1.95	0.001	1.57	1.2-2.05	0.005	1.5	1.13-1.99	0.006	1.44	1.11-1.86

Abbreviations: HR: hazard ratio; CI: confidence interval; RI: relapse incidence; MUD: matched unrelated donor; MSD: matched sibling donor; SCT: stem cell transplantation; AML: acute myeloid leukemia; CR2/3: subsequent remission; CR1: first remission; KPS: Karnofksy performace status; RIC: reduced-intensity conditioning; MAC: myeloablative conditioning; TCD: T-cell depletion; CMV: cytomegalovirus; CK: complex karyotype; MK: monosomal karyotype; -5/5q-: monosomy 5 or deletion 5q; abn(17p): 17p abnormalities; inv(3): inversion of chromosome 3; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; GRFS: graft-versus-host and relapse-free survival.

Table 4

Multivariate analysis using a Cox proportional hazard model including cytogenetic subgroups for RI, NRM, LFS, OS and GRFS.

	RI			NRM			LFS			OS			GRFS		
	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI
Age (per 10 year)	0.55	0.98	0.9-1.06	0.53	1.04	0.92-1.18	0.78	0.99	0.93-1.06	0.79	1.01	0.94-1.08	0.84	0.99	0.93-1.06
MUD vs MSD	0.06	0.82	0.67-1.01	0.004	1.61	1.16-2.24	0.98	1.00	0.84-1.19	0.39	1.08	0.9-1.3	0.8	0.98	0.83-1.15
Year of SCT	0.2	0.99	0.96-1.01	0.09	0.97	0.94-1.01	0.05	0.98	0.96-1.00	0.11	0.98	0.96-1.00	0.05	0.98	0.97-1.00
Secondary AML vs de novo	0.7	0.96	0.76-1.21	0.00005	1.87	1.38-2.54	0.06	1.2	1.00-1.44	0.01	1.27	1.05-1.53	0.09	1.17	0.98-1.4
CR2/3 vs CR1	0.58	1.14	0.71-1.82	0.0005	2.37	1.46-3.84	0.009	1.56	1.12-2.18	0.012	1.56	1.1-2.21	0.04	1.42	1.03-1.97
Active disease vs CR1	<0.00001	1.7	1.4-2.07	0.004	1.55	1.15-2.1	<0.00001	1.65	1.40-1.95	<0.00001	1.63	1.38-1.93	<0.00001	1.52	1.3-1.77
KPS≥80%	0.41	0.85	0.58-1.25	<0.00001	0.36	0.23-0.56	0.0009	0.62	0.47-0.82	0.00007	0.56	0.42-0.74	0.002	0.64	0.49-0.85
RIC vs MAC	0.26	1.12	0.92-1.37	0.16	1.25	0.92-1.69	0.06	1.18	1.00-1.39	0.14	1.14	0.96-1.35	0.07	1.16	1.00-1.37
Female to Male	0.87	1.02	0.8-1.3	0.1	1.34	0.95-1.88	0.31	1.11	0.91-1.35	0.2	1.14	0.93-1.39	0.11	1.17	0.97-1.41
In vivo TCD	0.95	1.01	0.82-1.24	0.12	0.78	0.57-1.07	0.41	0.93	0.78-1.11	0.36	0.92	0.77-1.1	0.007	0.8	0.68-0.94
Patient CMV+	0.33	0.91	0.75-1.1	0.78	1.04	0.77-1.41	0.52	0.95	0.8-1.12	0.53	0.95	0.8-1.12	0.25	0.91	0.78-1.07
Donor CMV+	0.41	1.08	0.9-1.31	0.83	0.97	0.72-1.3	0.59	1.05	0.89-1.23	0.44	1.07	0.9-1.26	0.73	0.97	0.84-1.13
-7/-7± CK (reference)		1			1			1			1			1	
-7/-7± CK	0.006	1.54	1.13-2.09	0.53	0.88	0.6-1.3	0.05	1.26	1.00-1.60	0.19	1.18	0.92-1.51	0.06	1.24	0.99-1.55
MK group	0.00003	2.02	1.45-2.82	0.47	1.17	0.76-1.82	0.0002	1.66	1.28-2.16	0.0008	1.6	1.22-2.1	0.00003	1.70	1.33-2.19
-5/5q- group	<0.00001	2.62	1.88-2.68	0.59	1.14	0.71-1.84	<0.00001	2.00	1.52-2.61	<0.00001	2.0	1.51-2.64	<0.00001	1.94	1.5-2.5
Abn(17p) group	<0.0001	3.76	2.67-5.3	0.12	1.48	0.9-2.44	<0.00001	2.78	2.11-3.67	<0.00001	2.74	2.05-3.65	<0.00001	2.47	1.9-3.22
Inv(3) group	<0.0001	3.47	2.42-4.97	0.72	1.11	0.63-1.98	<0.00001	2.45	1.82-3.29	<0.00001	2.21	1.63-3.00	<0.00001	2.27	1.71-3.01

Abbreviations: HR: hazard ratio; CI: confidence interval; MUD: matched unrelated donor; MSD: matched sibling donor; SCT: stem cell transplantation; AML: acute myeloid leukemia; CR2/3: subsequent remission; CR1: first remission; KPS: Karnofsky's performance status; RIC: reduced-intensity conditioning; MAC: myeloablative conditioning regimen; TCD: T-cell depletion; CMV: cytomegalovirus; RI: relapse incidence; abn(17p): abnormalities of chromosome 17p; CK: complex karyotype; MK: monosomal karyotype; -5/5q-: monosomy 5 or deletion 5q; inv(3) : inversion of chromosome 3; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; GRFS: graft-versus-host and relapse-free survival.