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This is the final version of the manuscript. It is the peer reviewed version of the following article:

Hemmati, P. G., Terwey, T. H., Na, I.-K., le Coutre, P., Jehn, C. F., Vuong, L. G., Dörken, B. and Arnold, R. (2015), Impact of early remission by induction therapy on allogeneic stem cell transplantation for acute myeloid leukemia with an intermediate-risk karyotype in first complete remission. Eur J Haematol, 94: 431–438. doi:10.1111/ejh.12449

which has been first published online on 11 October 2014 and in final form in:

European Journal of Haematology
2015 MAY; 94(5): 431-438
doi: 10.1111/ejh.12449

Publisher: Wiley-Blackwell

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Impact of early remission by induction therapy on allogeneic stem cell transplantation for acute myeloid leukemia with an intermediate risk karyotype in first complete remission

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Running Title Early remission in AML undergoing alloSCT in CR1

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Abstract

For patients with acute myeloid leukemia (AML) early achievement of remission during induction treatment is an important predictor for long-term outcome irrespective of the type of consolidation therapy employed. Here, we retrospectively examined the prognostic impact of early remission (ER) *versus* delayed remission (DR) in a cohort of 132 AML patients with an intermediate risk karyotype undergoing allogeneic stem cell transplantation (alloSCT) in first complete remission (CR1). In contrast to patients showing DR, patients achieving ER had a significantly higher 3-year overall survival (OS) and disease-free survival (DFS) of 76% *versus* 54% (p=0.03) and 76% *versus* 53% (p=0.03). Likewise, three years after alloSCT the cumulative incidence of relapse (CI-R) was significantly lower in the ER subgroup as compared to patients achieving DR, i.e. 10% *versus* 35% (p=0.004), whereas non-relapse mortality (NRM) did not differ significantly. Multivariate analysis identified DR as an independent prognosticator for an inferior DFS (HR 3.37, p=0.002) and a higher CI-R (HR 3.55, p=0.002). Taken together, these data may indicate that the rapid achievement of remission predicts a favorable outcome in patients with intermediate risk AML undergoing alloSCT in CR1. In turn, the adverse effect of DR may not be fully overcome by alloSCT.

Key words: allogeneic stem cell transplantation, acute myeloid leukemia, early remission, reduced intensity conditioning

Introduction

AML is a highly heterogeneous disease and despite tremendous progress in understanding and treating this disorder has been made within the last decades, only a minor proportion of patients will be ultimately cured by conventional therapeutic approaches (1, 2). AlloSCT is the most effective treatment option for AML and, therefore, has become standard of care for the majority of medically fit patients with non-favorable risk disease if a human leukocyte antigen (HLA)-compatible donor is available (2-4). Nonetheless, as compared to conventional post-remission therapy, alloSCT is associated with a considerable risk of NRM, which may outweigh the potential survival advantage.

In addition to patient-related variables such as comorbidities or physical performance, risk assessment in AML primarily includes pre-treatment disease-specific factors, e.g. genetic features, initial leukemic cell burden, preceding hematologic disorders such as myelodysplastic syndrome (MDS) or chronic myeloproliferative neoplasia (MPN), or a history of chemo- or radiation therapy. In addition, response to treatment was shown to predict outcome. As such, the rapid achievement of remission by induction therapy has long been recognized as a prognosticator for overall outcome (5-7). Likewise, early blast clearance, as determined one week after the first course of induction chemotherapy, predicts CR rate and has major prognostic relevance irrespective of the type of post-remission therapy (8-11). However, the impact of achieving early remission, i.e. absence of leukemic blasts in the bone marrow at the end of the first course of induction therapy, *versus* delayed remission on the outcome of patients with AML undergoing alloSCT has not yet been specifically explored. We therefore addressed this question in cohort of 132 consecutive patients with AML and an intermediate cytogenetic risk profile transplanted in CR1 at our center between 1994 and 2013.

Patients and Methods

Study design and data collection

Base-line characteristics and post-transplant follow-up data of all patients were prospectively collected in a computer database. 132 consecutive patients with AML and an intermediate cytogenetic risk profile according to the definition of the Southwestern Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG) (12) transplanted in CR1 at our center between 1994 and 2013 were retrospectively analyzed. All procedures were approved by the local ethics committee and are in full accordance with the Helsinki Declaration of 1975. Informed consent was obtained from all patients.

Patients and treatment characteristics

Patients and treatment characteristics are detailed in **Table 1**. The entire cohort (N=132) was divided into patients who achieved ER (N=79) or DR (N=53). Before referral to our transplant center, all patients were treated in a German multicenter AML trial. All patients aged <60 years (N=113) were treated according to the double induction strategy (13). In this cohort, the first course consisted of either daunorubicin 60 mg/m² or idarubicin 12 mg/m² for 3 days and cytarabine 100-200 mg/m² as a continuous infusion for 7 days ("7+3" regimen). Thereafter all patients received either one additional course of the same "7+3" regimen (N=4) or one course of a high-dose cytarabine (HD-AraC) (3000 mg/m²) regimen (N=109). All patients aged ≥60 years (N=19) were treated with a single course of "7+3" induction therapy. In case of more than 5% residual leukemic blasts in the bone marrow on day +16, induction was followed by either one additional course of the same regimen (N=5) one course of a HD-AraC (1000 mg/m^2) regimen (N=14). Depending on the scheduling of alloSCT, e.g. availability of an HLA-compatible donor, one (N=78) or two (N=7) additional courses HD-AraC (3000 mg/m^2 for patients aged <60 years or 1000 mg/m^2 for patients aged ≥60 years) consolidation were given as early as 2 to 4 weeks after achievement of CR. In all patients, remission status was assessed at day +16 and day +28 after begin of induction therapy by conventional cytology, multicolor flow-cytometry, and histology. ER was defined as a marrow blast count below 5% at day +16 and DR was defined as marrow blast count below 5% after the second course of induction therapy.

Two weeks before begin of conditioning CR1 was confirmed by bone marrow analysis. As described previously, standard MAC consisted of 6 x 2 Gy total body irradiation (TBI) and 2 x 60 mg/kg cyclophosphamide (14, 15). Patients with an HLA-mismatch received 3 x 10 mg/kg anti-thymocyte globulin (ATG) (Fresenius). Patients with contraindications against MAC, i.e. age >55 years, a history of proven or probable invasive fungal infection, previous severe non-fungal infections, or impaired cardiac, renal, or pulmonary function, were treated with RIC, which consisted of 6 x 30 mg/m^2 fludarabine, 2 x 4 mg/kg oral busulfan, and 4 x 10 mg/kg ATG (Fresenius) (14, 15). Transplants were from related (n = 60) or unrelated (n = 72) donors and were HLA-matched (10/10 antigens) (n = 119) or HLA-mismatched (n = 13) according to high-resolution molecular typing.

Prophylaxis of graft-*versus*-host disease and supportive care

Prophylaxis of graft-*versus*-host disease (GvHD) consisted of either cyclosporine A and short course methotrexate for MAC patients or CSA and mycophenolate mofetil for RIC patients as described in detail previously (14). Acute GvHD (aGvHD) and chronic GvHD (cGvHD) were graded according to standard criteria (16). Whereas patients with aGvHD °I received topical treatment only, therapy of aGvHD °II-IV consisted of prednisolone (starting dose: 2 mg/kg) for 7 days, which was then gradually tapered according to the individual response. All patients received prophylactic ciprofloxacin, amphotericin B suspension, and aciclovir until

neutrophil counts reached 1 x 10^9/l. In patients with a platelet count of ≥50 x 10^9/l prophylactic cotrimoxazole was started at day +28 following alloSCT. Polyvalent immunoglobulins were administered bi-weekly until day +90 in patients with a total IgG below 5 g/l (14).

Statistical analyses

Statistical analyses were performed using NCSS 2007 (NCSS; Kayville, UT, USA) and SPSS 14 (SPSS; Chicago, IL, USA) as of September 30th, 2013. Fisher's exact test and χ^2 test were used for comparing categorical data. Survival data (OS and DFS) were calculated according to Kaplan-Meier and tested univariately by log-rank test. Statistical significance was assessed at the $p<0.05$ level (two-sided). NRM and relapse are given as cumulative incidences calculated in a competing-risks setting (17). Cox proportional hazard regression model was used for univariate and multivariate analyses and included the following variables: AML subtype, age group, era of alloSCT, interval from diagnosis to alloSCT, extramedullary disease, Karnofsky performance status (KPS), type of conditioning, donor type/HLA-match, and stem cell source. First, a univariate model was calculated for all parameters. Thereafter, forward and backward selection (inclusion p=0.05, exclusion p=0.10) was applied. By definition, the lowest risk category within a group was assigned a hazard ratio (HR) of 1 and used as a reference. HRs are given with a 95% confidence interval (CI) and corresponding p-values are shown.

Results

Overall outcome

After a median follow-up of 56 (4-220) months for the surviving patients, 87 patients (66%) are alive and in CR. A relapse occurred in 26 patients (20%) after a median interval of 8 (1-133) months, whereas 19 patients (14%) died from NRM. 47 patients (36%) had no aGvHD, whereas 27 (20%) or 58 patients (44%) developed °I or °II-IV aGvHD. Chronic GvHD was absent in 65 patients (49%) and limited or extensive chronic cGvHD occurred in 40 (30%) or 27 patients (21%). Projected OS (95% CI) or DFS (95% CI) of the entire cohort after 1, 3, 5, and 10 years was 81% (74-88%), 68% (59-75%), 65% (56-74%), and 61% (49-73%) or 75% (67-83%), 68% (59-76%), 65% (56-74%), and 59% (47-71%). At the same time points the cumulative incidence of relapse (CI-R) (95% CI) or non-relapse mortality (CI-NRM) (95% CI) was 12% (8-20%), 19% (13-28%), 22% (15-32%), and 22% (15-32%) or 13% (8-20%), 13% (8-20%), 13% (8-20%), and 17% (10-31%).

Outcome according to remission status after the first course of induction therapy

We next analyzed OS, DFS, CI-R, and CI-NRM according to the remission status after the first course of induction therapy. Specifically, 79 patients (60%) achieved ER defined as bone marrow blast <5% at day +16 after the first course of induction therapy, whereas 53 patients (40%) had a DR, i.e. first hematologic remission was achieved after two cycles of induction therapy. As shown in **Table 1**, there were no statistically significant differences with regards to gender, age group, AML subtype, transplant era, extramedullary disease, time from diagnosis to transplantation, KPS, donor type/HLA-match, conditioning regimen, or stem cell source between the ER and the DR subgroup. As displayed in **Figure 1**, patients who achieved ER had a significantly higher OS as compared to patients displaying DR (p=0.0313). Likewise, ER predicted a significantly lower relapse incidence CI-R (p=0.004). No statistically significant differences in CI-NRM between the two subgroups were found (p=0.638).

Uni- and multivariate analysis

To further analyze the prognostic impact of ER *versus* DR we performed univariate analyses by using the Cox proportional hazard regression model. In addition to remission status, a number of other factors were analyzed in parallel. As shown in **Table 2**, DR was associated with an inferior OS and DFS as well as an increased relapse rate. Similarly, a KPS of ≤80% was predictive of a lower OS and DFS. Specifically, patients with a KPS of ≤80% had a higher risk of relapse, whereas the CI-NRM was not elevated as compared to patients with a KPS >80%. Patients transplanted from a mismatched unrelated donor (mMUD) had an inferior OS and DFS as compared to patients with a matched related or unrelated donor. Furthermore, patients with AML evolving from MPN or MDS as well as patients with therapy-related AML (tAML) had an inferior survival as compared to patients with *de novo* AML. All other factors examined were not predictive for OS, DFS, CI-R, or CI-NRM.

Next, multivariate analysis was performed. As shown in **Table 3**, DR was associated with a significantly lower DFS and a higher CI-R. A KPS of ≤80% was an independent prognosticator for a lower OS. None of the factors examined was predictive for NRM (data not shown).

Outcome according to type of conditioning

Finally, we analyzed whether the type of conditioning therapy impacts on overall outcome and relapse incidence in patients achieving ER as compared to patients displaying DR (**Table 4**). Neither in the ER nor in the DR subgroup a statistically significant difference in OS, DFS, or CI-R between patients treated with MAC or RIC was found. In particular, relapse risk was not elevated in patients displaying DR undergoing RIC-alloSCT.

Discussion

The analysis of 132 consecutive patients with AML and an intermediate cytogenetic risk profile who underwent alloSCT in CR1 at our center suggests, that achieving ER as compared to DR is associated with a favorable overall outcome. Importantly, we demonstrate that the beneficial effect of ER *versus* DR with regards to DFS and relapse incidence is maintained in multivariate analysis, which suggests that it has independent prognostic value. Furthermore, achieving ER strongly correlates with early blast clearance, which was shown before to be predictive for overall outcome of patients with AML irrespective of the type of post-remission therapy (8-11). In general, our data underline the importance of treatment response for generating an integrated risk-profile which, therefore, should be incorporated into a decision algorithm for patients with AML as has been proposed recently by the European Leukemia Network (3). Furthermore, our data implicate that the adverse effect of failure to achieve ER is not fully overcome by alloSCT even in patients entering CR after a consecutive course of induction therapy. A recent analysis reported by the ECOG suggests that patients entering remission after one or two cycles of induction have a similar prognosis (18). However, this cohort was heterogeneous with respect to cytogenetic risk group and type of post-remission therapy, i.e. transplant *versus* conventional therapy, which may explain the discrepancy.

Patients reaching ER are characterized by a remarkably low relapse incidence, which is in the range of 10-15% at 10 years after alloSCT. Likewise, NRM levels off around 10-15% as early as 18 months post-transplant and remains stable thereafter. In principle, these results underline that alloSCT is not only feasible in this setting, but highly effective and safe. Consequently, alloSCT should be considered as first choice post-remission treatment option

for medically fit patients with intermediate-risk AML entering CR1 if an HLA-compatible donor is available. In this regard, our results are in line with a number of recently published studies reporting data from donor-*versus*-no donor comparisons, matched pair analyses, and randomized phase-III multicenter clinical trials (3, 19-22). Nonetheless, it might be of interest to address whether the speed of achieving remission, i.e. ER *versus* DR, is of prognostic relevance in other genetic risk groups of AML patients undergoing alloSCT in CR1 as well.

In contrast, both OS and DFS are significantly reduced in patients showing DR albeit CR1 was reached after a second induction cycle is administered. This is due to a considerably higher relapse incidence reaching a plateau of close to 40% at five years after alloSCT. It is obvious to assume that occult populations of leukemic cells outlasting two or more courses of induction/consolidation therapy are the primary source of disease recurrence in this situation. Indeed, two recently published analyses using pre-transplant minimal residual disease (MRD) monitoring suggest that even minute populations of residual leukemic cells, e.g. below <0.1% as detected by multicolor flow-cytometry, in patients achieving morphologic CR prior to alloSCT give rise to relapse and, thereby, have a tremendous impact on overall outcome (23, 24). Specifically, 3-year OS declines to around 30% in MRD-positive patients as compared to 75% in patients MRD-negative pre-transplant. In our cohort, data pre-transplant MRD were available in only 53/132 patients. In the subgroup of MRD-negative patients (N=33) 4 relapses occurred, whereas in 8/20 MRD-positive patients relapsed after alloSCT (p=0.007). However, due to the limited number of patients in each subgroup we are unable to interpret pre-transplant MRD in the context of ER *versus* DR. Nonetheless, this inevitably brings up the question how to tackle the dilemma of failure to achieve an early and/or molecular CR before proceeding to alloSCT. One approach could be to apply repetitive courses of consolidation chemotherapy until MRD negativity is reached. A recently published analysis of EBMT registry data clearly indicates that, at least for patients with AML undergoing RIC-alloSCT in CR1, consolidation therapy neither reduces the risk of relapse, nor improves overall outcome (25). One should assume that the results in patients undergoing alloSCT following MAC are similar. Alternatively, risk-adapted post-transplant management, e.g. early cessation of immunosuppressive therapy and/or the use adoptive immunotherapy to fully exploit the beneficial graft-*versus*-leukemia (GvL) effect might serve to overcome the risk of therapeutic failure in this situation (26-28). This strategy is supported by the observation that the occurrence of GvHD reduces the risk of disease recurrence irrespective of the presence or absence or MRD (24). Furthermore, novel therapeutics such as hypomethylating agents might be used to prevent relapse by enhancing the GvL effect (29, 30). In any event, despite the higher relapse risk in patients who, in addition of being in hematologic remission, do not meet more stringent response criteria, e.g. MRD negativity, after two courses of induction chemotherapy, alloSCT should not be withheld, because the results with conventional post-remission therapy is dismal.

In patients showing delayed remission during induction therapy, intensive conditioning such as a myeloablative approach might be compensatory by effectively eradicating residual leukemic cells in the recipient prior to allografting. Therefore, we analyzed overall outcome and relapse incidence according to the type of conditioning in both the ER and the DR subgroup. However, we failed to reveal any significant differences between patients treated with either MAC or RIC prior to alloSCT. Specifically, OS and relapse incidence were not lowered by MAC as compared to RIC in the DR group. Yet, the number of patients in each subgroup is small and, therefore, data must be interpreted with due caution. Analyzing larger data sets should allow for answering this important question.

Despite the limitations of a retrospective analysis in a rather small cohort of patients, our data indicate that achieving early remission by induction therapy is an independent predictor for overall outcome in patients with AML and an intermediate risk karyotype transplanted in

CR1. In turn, delayed remission is associated with an adverse outcome and, therefore, should prompt for maneuvers to counteract the high risk of disease recurrence. In addition to transplantion-specific options, e.g. rapid tapering of immunosuppression and the administration of donor lymphocyte infusions (DLI), these may also include the use of novel therapeutics including hypomethylating agents or, when applicable, mulitkinase inhibitors, e.g. in FLT3-ITD positive AML, in the post-transplant setting (31, 32). Furthermore, innovative strategies to detect and treat an impeding relapse after transplant as early as possible are clearly warranted in the future.

Acknowledgements

We thank Sabine Diehl and Doreen Uhlenbroch for excellent data management as well as the nursing team for delivering superb patient care.

Conflict of interest

The authors declare no conflict of interest.

References

1. Miller CA, Wilson RK, Ley TJ. Genomic landscapes and clonality of de novo AML. N Engl J Med. 2013; **369**(15): 1473.
2. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. Lancet. 2013; **381**(9865): 484-95.
3. Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhäuser M, Juliusson G, Racil Z, Rowe JM, Russell N, Mohty M, Löwenberg B, Socie G, Niederwieser D, Ossenkoppele GJ. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. Nat Rev Clin Oncol. 2012; **9**(10): 579-90.
4. Estey EH. How to manage high-risk acute myeloid leukemia. Leukemia. 2012; **26**(5): 861-9.
5. Büchner T, Urbanitz D, Hiddemann W, Rühl H, Ludwig WD, Fischer J, Aul HC, Vaupel HA, Kuse R, Zeile G, et al. Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. J Clin Oncol. 1985; **3**(12): 1583-9.
6. Estey EH, Shen Y, Thall PF. Effect of time to complete remission on subsequent survival and disease-free survival time in AML, RAEB-t, and RAEB. Blood. 2000; **95**(1): 72-7.
7. Preisler HD, Priore R, Azarnia N, Barcos M, Raza A, Rakowski I, Vogler R, Winton EL, Browman G, Goldberg J, et al. Prediction of response of patients with acute nonlymphocytic leukaemia to remission induction therapy: use of clinical measurements. Br J Haematol. 1986; **63**(4): 625-36.
8. Büchner T, Hiddemann W, Wörmann B, Löffler H, Gassmann W, Haferlach T, Fonatsch C, Haase D, Schoch C, Hossfeld D, Lengfelder E, Aul C, Heyll A, Maschmeyer G, Ludwig WD, Sauerland MC, Heinecke A. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood. 1999; **93**(12): 4116-24.
9. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, Rees JK, Stevens RF, Walker H. A simple, robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. Br J Haematol. 1999; **107**(1): 69-79.
10. Kern W, Voskova D, Schoch C, Schnittger S, Hiddemann W, Haferlach T. Prognostic impact of early response to induction therapy as assessed by multiparameter flow cytometry in acute myeloid leukemia. Haematologica. 2004; **89**(5): 528-40.
11. Kern W, Haferlach T, Schoch C, Löffler H, Gassmann W, Heinecke A, Sauerland MC, Berdel W, Büchner T, Hiddemann W. Early blast clearance by remission induction therapy is a major independent prognostic factor for both achievement of complete remission and long-term outcome in acute myeloid leukemia: data from the German AML Cooperative Group (AMLCG) 1992 Trial. Blood. 2003; **101**(1): 64-70.
12. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, Paietta E, Willman CL, Head DR, Rowe JM, Forman SJ, Appelbaum FR. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000; **96**(13): 4075-83.
13. Büchner T, Schlenk RF, Schaich M, Döhner K, Krahl R, Krauter J, Heil G, Krug U, Sauerland MC, Heinecke A, Spath D, Kramer M, Scholl S, Berdel WE, Hiddemann W, Hoelzer D, Hehlmann R, Hasford J, Hoffmann VS, Döhner H, Ehninger G, Ganser A, Niederwieser DW, Pfirrmann M. Acute Myeloid Leukemia (AML): different treatment strategies versus a common

standard arm--combined prospective analysis by the German AML Intergroup. J Clin Oncol. 2012; **30**(29): 3604-10.

14. Hemmati PG, Terwey TH, Massenkeil G, le Coutre P, Vuong LG, Neuburger S, Dörken B, Arnold R. Reduced intensity conditioning prior to allogeneic stem cell transplantation in first complete remission is effective in patients with acute myeloid leukemia and an intermediate-risk karyotype. Int J Hematol. 2010; **91**(3): 436-45.
15. Terwey TH, Vega-Ruiz A, Hemmati PG, Martus P, Dietz E, le Coutre P, Massenkeil G, Dörken B, Arnold R. NIH-defined graft-versus-host disease after reduced intensity or myeloablative conditioning in patients with acute myeloid leukemia. Leukemia. 2012; **26**(3): 536-42.
16. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW, Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005; **11**(12): 945-56.
17. Hemmati PG, Terwey TH, le Coutre P, Vuong LG, Massenkeil G, Dörken B, Arnold R. A modified EBMT risk score predicts the outcome of patients with acute myeloid leukemia receiving allogeneic stem cell transplants. Eur J Haematol. 2011; **86**(4): 305-16.
18. Rowe JM, Kim HT, Cassileth PA, Lazarus HM, Litzow MR, Wiernik PH, Tallman MS. Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. Cancer. 2010; **116**(21): 5012-21.
19. Nagler A, Rocha V, Labopin M, Unal A, Ben Othman T, Campos A, Volin L, Poire X, Aljurf M, Masszi T, Socie G, Sengelov H, Michallet M, Passweg J, Veelken H, Yakoub-Agha I, Shimoni A, Mohty M. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen--a report from the acute leukemia working party of the European group for blood and marrow transplantation. J Clin Oncol. 2013; **31**(28): 3549-56.
20. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, Wadleigh M, DeAngelo DJ, Stone RM, Sakamaki H, Appelbaum FR, Döhner H, Antin JH, Soiffer RJ, Cutler C. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. Jama. 2009; **301**(22): 2349-61.
21. Cornelissen JJ, Breems D, van Putten WL, Gratwohl AA, Passweg JR, Pabst T, Maertens J, Beverloo HB, van Marwijk Kooy M, Wijermans PW, Biemond BJ, Vellenga E, Verdonck LF, Ossenkoppele GJ, Löwenberg B. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. J Clin Oncol. 2012; **30**(17): 2140-6.
22. Stelljes M, Krug U, Beelen DW, Braess J, Sauerland MC, Heinecke A, Ligges S, Sauer T, Tschanter P, Thoennissen GB, Berning B, Kolb HJ, Reichle A, Holler E, Schwerdtfeger R, Arnold R, Scheid C, Muller-Tidow C, Woermann BJ, Hiddemann W, Berdel WE, Buchner T. Allogeneic transplantation versus chemotherapy as postremission therapy for acute myeloid leukemia: a prospective matched pairs analysis. J Clin Oncol. 2014; **32**(4): 288-96.
23. Walter RB, Gooley TA, Wood BL, Milano F, Fang M, Sorror ML, Estey EH, Salter AI, Lansverk E, Chien JW, Gopal AK, Appelbaum FR, Pagel JM. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. J Clin Oncol. 2011; **29**(9): 1190-7.
24. Walter RB, Buckley SA, Pagel JM, Wood BL, Storer BE, Sandmaier BM, Fang M, Gyurkocza B, Delaney C, Radich JP, Estey EH, Appelbaum FR. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. Blood. 2013; **122**(10): 1813-21.

25. Yeshurun M, Labopin M, Blaise D, Cornelissen JJ, Sengeloev H, Vindelov L, Kuball J, Chevallier P, Craddock C, Socie G, Bilger K, Schouten HC, Fegueux N, Goker H, Maertens J, Bunjes D, Arnold R, Nagler A, Mohty M. Impact of postremission consolidation chemotherapy on outcome after reduced-intensity conditioning allogeneic stem cell transplantation for patients with acute myeloid leukemia in first complete remission: A report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Cancer. 2014; **120**(6): 855-63.

26. Baron F, Labopin M, Niederwieser D, Vigouroux S, Cornelissen JJ, Malm C, Vindelov LL, Blaise D, Janssen JJ, Petersen E, Socie G, Nagler A, Rocha V, Mohty M. Impact of graft-versus-host disease after reduced-intensity conditioning allogeneic stem cell transplantation for acute myeloid leukemia: a report from the Acute Leukemia Working Party of the European group for blood and marrow transplantation. Leukemia. 2012; **26**(12): 2462-8.

27. Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, Frassoni F, Boiron JM, Yin JL, Finke J, Shouten H, Blaise D, Falda M, Fauser AA, Esteve J, Polge E, Slavin S, Niederwieser D, Nagler A, Rocha V. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia. 2005; **19**(12): 2304-12.

28. Valcarcel D, Martino R, Caballero D, Martin J, Ferra C, Nieto JB, Sampol A, Bernal MT, Pinana JL, Vazquez L, Ribera JM, Besalduch J, Moraleda JM, Carrera D, Brunet MS, Perez-Simon JA, Sierra J. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J Clin Oncol. 2008; **26**(4): 577-84.

29. Choi J, Ritchey J, Prior JL, Holt M, Shannon WD, Deych E, Piwnica-Worms DR, DiPersio JF. In vivo administration of hypomethylating agents mitigate graft-versus-host disease without sacrificing graft-versus-leukemia. Blood. 2010; **116**(1): 129-39.

30. Jabbour E, Giralt S, Kantarjian H, Garcia-Manero G, Jagasia M, Kebriaei P, de Padua L, Shpall EJ, Champlin R, de Lima M. Low-dose azacitidine after allogeneic stem cell transplantation for acute leukemia. Cancer. 2009; **115**(9): 1899-905.

31. Metzelder SK, Schroeder T, Finck A, Scholl S, Fey M, Götze K, Linn YC, Kröger M, Reiter A, Salih HR, Heinicke T, Stuhlmann R, Müller L, Giagounidis A, Meyer RG, Brugger W, Vohringer M, Dreger P, Mori M, Basara N, Schäfer-Eckart K, Schultheis B, Baldus C, Neubauer A, Burchert A. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. Leukemia. 2012; **26**(11): 2353-9.

32. Schroeder T, Czibere A, Platzbecker U, Bug G, Uharek L, Luft T, Giagounidis A, Zohren F, Bruns I, Wolschke C, Rieger K, Fenk R, Germing U, Haas R, Kröger N, Kobbe G. Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. Leukemia. 2013; **27**(6): 1229-35.

	Early remission Number (%) N=79	**Delayed remission Number (%) N=53**	***P***
Gender			*0.81*
Male	36 (46)	23 (43)	
Female	43 (54)	30 (57)	
Median age, years (range)	48 (17-70)	47 (19-70)	*0.78*
Age group			*0.24*
<40 years	29 (37)	14 (26)	
40-60 years	33 (42)	30 (57)	
>60 years	17 (21)	9 (17)	
AML subtype			*0.76*
De novo AML	60 (76)	39 (74)	
Other	19 (24)	14 (26)	
Year of alloSCT			*0.10*
1994 – 2004	19 (24)	16 (30)	
2005 – 2010	37 (47)	15 (28)	
2011 – 2013	23 (29)	22 (42)	
Extramedullary disease			*0.47*
Absent	70 (89)	49 (92)	
Present	9 (11)	4 (8)	
Induction/consolidation courses applied before alloSCT*			*0.57*
2	31 (39)	16 (30)	
3	44 (56)	34 (64)	
>3	4 (5)	3 (6)	
Early blast clearance			***<0.001***
Yes	76 (96)	2 (4)	
No	3 (4)	51 (96)	
Interval from diagnosis to SCT			*0.37*
< 6 months	37 (47)	29 (55)	
≥ 6 months	42 (53)	24 (45)	
Karnofsky Performance Status			*0.53*
100 – 90%	70 (89)	45 (85)	
≤ 80%	9 (11)	8 (15)	
Donor type			*0.95*
MRD	35 (44)	25 (47)	
MUD	36 (46)	23 (43)	
mMUD	8 (10)	5 (10)	
Type of conditioning			*0.41*
MAC	37 (47)	21 (40)	
RIC	42 (53)	32 (60)	
Stem cell source			*0.58*
Bone marrow	8 (10)	7 (13)	
Peripheral blood stem cells	71 (90)	46 (87)	
Donor Lymphocyte Infusion			*0.39*
No	71 (90)	45 (85)	
Yes	8 (11)	8 (15)	

Table 1: Patients and treatment characteristics.
The entire cohort (N=132) was subdivided in patients who achieved early blast clearance (ER) (N=79) or delayed blast clearance (DR) (N=53). Abbreviations: alloSCT: allogeneic stem cell transplantation, AML: acute myeloid leukemia, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, MRD: matched related donor, MUD: matched unrelated donor, mMUD: mismatched unrelated donor. * All patients received at least one course of high-dose cytarabine (HD-AraC), i.e. either during induction or consolidation therapy.

	No. of patients (%)	OS HR (95% CI)	*P*	DFS HR (95% CI)	*P*	Relapse HR (95% CI)	*P*	NRM HR (95% CI)	*P*
Age group									
<40 years	43 (33)	1.0		1.0		1.0		1.0	
40-60 years	63 (48)	1.21 (0.60-2.46)	*0.592*	1.23 (0.61-2.50)	*0.561*	1.26 (0.51-3.11)	*0.616*	1.20 (0.39-3.71)	*0.751*
>60 years	26 (19)	1.63 (0.69-3.88)	*0.271*	1.58 (0.66-3.75)	*0.301*	1.52 (0.49-4.72)	*0.473*	1.67 (0.44-6.40)	*0.451*
AML subtype									
De novo AML	99 (75)	1.0		1.0		1.0		1.0	*0.233*
Other	33 (25)	**1.97 (1.03-3.76)**	***0.040***	1.68 (0.87-3.24)	*0.124*	1.57 (0.65-3.79)	*0.315*	1.83 (0.68-4.96)	
Year of alloSCT									
1994 – 2004	35 (27)	1.0		1.0		1.0		1.0	
2005 – 2010	52 (39)	1.20 (0.57-2.55)	*0.634*	1.33 (0.62-2.87)	*0.461*	1.88 (0.67-5.27)	*0.232*	0.81 (0.25-2.64)	*0.720*
2011 – 2013	45 (34)	1.53 (0.64-3.68)	*0.333*	1.21 (0.50-2.91)	*0.670*	1.66 (0.49-5.65)	*0.421*	0.82 (0.24-2.83)	*0.752*
Extramedullary disease									
Absent	119 (90)	1.0		1.0		1.0		1.0	*0.733*
Present	13 (10)	0.62 (0.19-2.03)	*0.436*	0.44 (0.11-1.83)	*0.259*	1.03 (0.64-3.39)	*0.992*	1.29 (0.30-5.66)	
Remission									
Early remission (ER)	79 (60)	1.0		1.0		1.0		1.0	
Delayed remission (DR)	53 (40)	**1.92 (1.05-3.53)**	***0.035***	**1.89 (1.03-3.47)**	***0.040***	**3.32 (1.46-7.55)**	***0.004***	0.83 (0.31-2.26)	*0.721*
Intervall from diagnosis to SCT	66 (50)	1.0		1.0		1.0		1.0	
< 6 months	66 (50)	0.75 (0.41-1.39)	*0.360*	0.76 (0.41-1.40)	*0.381*	0.70 (0.32-1.55)	*0.381*	0.85 (0.33-2.21)	*0.745*
≥ 6 months									
Karnofsky Performance Status									
100 – 90%	115 (87)	1.0		1.0		1.0		1.0	
≤ 80%	17 (13)	**2.14 (1.02-4.48)**	***0.042***	**2.26 (1.08-4.74)**	***0.031***	**2.84 (1.13-7.11)**	***0.027***	1.59 (0.46-5.56)	*0.467*
Donor type									
MRD	60 (45)	1.0		1.0		1.0		1.0	
MUD	59 (45)	1.12 (0.58-2.19)	*0.730*	**1.21 (0.62-2.35)**	*0.579*	0.88 (0.37-2.10)	*0.774*	1.97 (0.66-5.94)	*0.227*
mMUD	13 (10)	**2.58 (1.07-6.29)**	***0.035***	**2.75 (1.13-6.68)**	***0.026***	2.34 (0.75-7.33)	*0.143*	3.75 (0.88-16.0)	*0.074*
Type of conditioning									
MAC	59 (45)	1.0		1.0		1.0		1.0	
RIC	74 (55)	1.20 (0.65-2.22)	*0.559*	1.19 (0.64-2.20)	*0.583*	0.95 (0.43-2.10)	*0.890*	1.70 (0.62-4.69)	*0.302*
Stem cell source									
Bone marrow	15 (11)	1.0		1.0		1.0		1.0	
Peripheral blood stem cells	117 (89)	0.73 (0.33-1.62)	*0.449*	0.68 (0.31-1.50)	*0.337*	0.51 (0.20-1.31)	*0.161*	1.20 (0.26-5.49)	*0.813*

Table 2: Univariate analysis.
Univariate analyses were performed using the Cox proportional hazard regression model. Hazard ratios (HR) with the 95% CI are given along with P-values for the comparison of the respective category with the first one. Variables with significant differences are bold-faced.

	No. of patients (%)	**OS HR (95% CI)**	***P***	**DFS HR (95% CI)**	***P***	**Relapse HR (95% CI)**	***P***
Remission							
Early remission (ER)	79 (59)			1.0		1.0	
Delayed remission (DR)	53 (41)			**3.37 (1.50-7.61)**	***0.002***	**3.55 (1.61-7.94)**	***0.002***
Karnofsky Performance Status							
100-90%	115 (87)	1.0					
≤ 80%	17 (13)	**2.58 (1.31-5.12)**	***0.007***				

Table 3: Multivariate Analysis.
Prognostic variables examined were age group, acute myeloid leukemia (AML) subtype, transplant era, extramedullary disease, blast clearance, interval from diagnosis to transplantation, Karnofsky-Performance Status, donor type and match, type of conditioning, and stem cell source. The P-values refer to the comparison of the respective category with the first one. Bold-faced text indicates parameters showing statistically significant differences.

	No. of patients (%)	**OS HR (95% CI)**	***P***	**DFS HR (95% CI)**	***P***	**Relapse HR (95% CI)**	***P***
Early remission							
MAC	38 (48)	1.0		1.0		1.0	
RIC	41 (52)	0.85 (0.35-2.07)	0.727	0.84 (0.34-2,04)	0.700	0.60 (0.14-2.42)	0.468
Delayed remission							
MAC	21 (41)	1.0		1.0		1.0	
RIC	32 (59)	1.51 (0.62-3.66)	0.366	1.53 (0.63-373)	0.346	1.07 (040-2.89)	0.897

Table 4: Outcome according to type of conditioning in ER *versus* DR patients.
Univariate analysis was performed by using the Cox proportional hazard regression model in the ER and the DR subgroup of patients treated with either RIC or MAC prior to alloSCT.

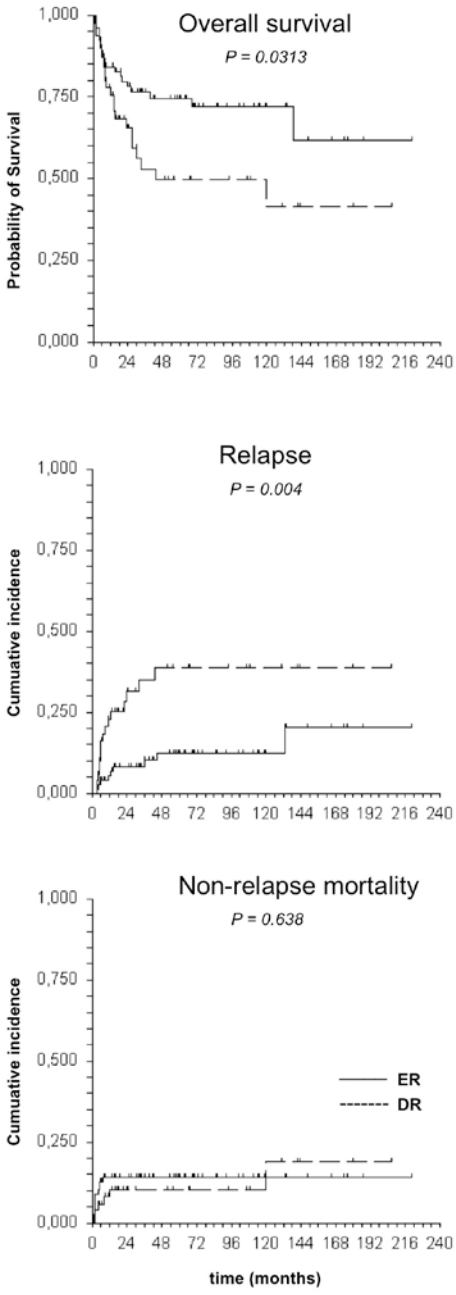

Figure 1

Figure 1: Outcome of alloSCT in patients achieving early remission (ER) *versus* delayed remission (DR). Overall survival (OS), cumulative incidence of relapse (CI-R) and non-relapse mortality (CI-NRM) were analyzed by Kaplan-Meier (OS) or calculated in a competing risk setting (CI-R, CI-NRM). In patients achieving early remission (ER) OS and CI-R is significantly better as compared to patients with delayed remission (DR), whereas no significant difference in NRM between the subgroups was found.