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ARTICLE

Low relapse risk in poor risk AML after conditioning with 10-day decitabine, fludarabine and 2 Gray TBI prior to allogeneic hematopoietic cell transplantation

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Abstract

Patients with poor risk acute myeloid leukemia (AML) have a dismal outcome. We hypothesized that combining decitabine with a standard non-myeloablative (NMA) conditioning regimen prior to allogeneic hematopoietic cell transplantation (allo HCT), might decrease the relapse incidence. We conducted a multicenter prospective phase II study (NCT02252107) with 10-day decitabine (20 mg/m^2/day) integrated in a standard non-myeloablative conditioning regimen (3 days fludarabine 30 mg/m^2 with 2 Gray total body irradiation (TBI)). Patients with AML ≥ 18 years in 1st (in)complete remission (CR/CRi) with a poor or very poor risk profile, as defined by the HOVON-132 protocol, were eligible. Results: Forty-six patients (median age 60; range 23–74) were included. Median follow up time was 44 months (range 31–65 months). The cumulative 1-year incidence of relapse and NRM were respectively 23% and 11%. Incidence of grade III-IV acute graft-vs-host-disease (GVHD) and severe chronic GVHD were 13% and 20%, respectively. One-year OS was 70%. Application of ELN 2017 risk classification to the study cohort revealed a cumulative one-year relapse rate of respectively 31% and 13% for the adverse and intermediate risk patients. To conclude, the 10-day DEC/FLU/TBI conditioning regimen prior to allo HCT in poor risk AML patients is effective and feasible.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with different molecular and genetic abnormalities, that define the various disease risk groups. Patients that pertain to an adverse or poor risk group have a dismal outcome, despite allogeneic hematopoietic cell transplantation (allo HCT), with a 5-year overall survival (OS) of 19–46% [1, 2]. This dismal outcome is mainly due to the high relapse rate (40–68%) in these patients. Choosing the optimal conditioning regimen prior to allo HCT is challenging and its choice is influenced by various factors, such as, age of the patient, performance status and comorbidities, disease risk, remission status at the time of transplantation, and donor type [3].

Over the past decade, many studies have been carried out on different conditioning approaches focused on reducing the relapse rate in conjunction with a low non-relapse mortality (NRM) rate. The Seattle team has introduced total body irradiation (TBI) (2 Gy) in combination with fludarabine (FLU) as a non-myeloablative (NMA) conditioning prior to allo HCT in older patients. A report on 274 AML patients conditioned with FLU-TBI 2 Gy has shown 26% NRM, 42% relapse and 37% survival [4]. Although this conditioning regimen is considered well suited for older patients with AML and comorbidities, it is currently considered a suboptimal regimen for many patients, because of the high risk of relapse.

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Comparison of myeloablative conditioning (MAC) with reduced intensity conditioning (RIC) regimens in patients with (poor risk) AML has yielded contradictory results [2, 5–11]. Some of these studies showed that higher relapse risk with RIC allo HCT was counterbalanced by higher NRM in MAC allo HCT, resulting in comparable OS. Although two recent studies showed superiority of the MAC conditioning regimen compared to the RIC conditioning regimen, this superiority was not apparent in patients with high risk disease and not in patients older than 60 years [7, 8]. Furthermore, measurable residual disease (MRD) at start of conditioning prior to allo HCT, has shown to be an important factor predicting relapse risk [6, 9–11], although not all of the studies pointed in the same direction regarding the question if MAC SCT would result in better outcome. So, AML patients with high risk disease and with MRD prior to start conditioning regimen currently have a high relapse rate, which is not overcome by MAC.

Apparently, novel treatment concepts are needed, especially for (unfit and/or MRD positive) AML patients with poor risk disease. We previously hypothesized that combining a NMA conditioning regimen with the hypomethylating agent (HMA) 5-aza-2′-deoxycitidine (decitabine) could be promising, especially since decitabine treatment had little extramedullary toxicity, has immune modulating properties and good efficacy against (high risk) AML [12]. In our pilot study with 10-day decitabine added to the NMA FLU/TBI regimen (DEC/FLU/TBI), we demonstrated that this conditioning regimen was feasible and effective [13]. One of the immune modulating actions of HMA is the upregulated expression of epigenetically silenced tumor-associated antigens (TAA) [14], which is interesting because these TAA are tumor-restricted and may have an immunogenic potential, that is important for the graft-vs-leukemia (GVL) effect. In our DEC/FLU/TBI pilot study several TAA- specific CD8(+) T cells were observed after allo HCT. We think this immunologic effect of decitabine making silenced TAA visible for the donor immune system, contributes to disease control post transplantation. Stimulated by our preliminary data with the DEC/FLU/TBI conditioning regimen we initiated this phase II study (NCT02252107). In this study we added 10 days of decitabine to the standard NMA conditioning with fludarabine/ 2 Gy TBI in patients with poor or very poor risk AML to reduce 1-year relapse rate.

Methods

Study design and patient selection

This prospective phase II, multicenter, single arm, intervention study was performed from October 2014 until October 2020 at the departments of Hematology of the Radboud University Medical Center Nijmegen (The Netherlands), the University Medical Center Groningen (The Netherlands) and the University of Liège (Belgium). Adult patients with poor or very poor risk AML were included if they were in first (in) complete remission at study entry (CR/CRi), and if eligible to receive an allo HCT. Poor risk AML was defined according to the HOVON-132 protocol (www.hovon.nl); i.e., abnormal karyotype (non core-binding factors) or white blood cell count (WBC) > 100×10^9/L or no early remission (i.e., CR after 1st cycle of intensive chemotherapy). Very poor risk AML was defined as AML with one or more of the following characteristics: monosomal karyotype, abnormal 3q26, EVI1 overexpression, *TP53* mutation, *RUNX1* mutation, *ASXL1* mutation or FLT3-ITD with a FLT3-ITD/FLT3wt ratio > 0.6. Patients with active and uncontrolled infections or infections with HIV, HBV, HCV were excluded. Patients were not eligible if they had received an hypomethylating agent before start of the study protocol, only "3 + 7" based remission induction schedules were allowed.

Study protocol

Patients received 10-day decitabine (20 mg/m^2/day) in addition to the NMA conditioning regimen, developed by the Fred Hutchinson Cancer Research Center (Seattle), consisting of 3 days fludarabine 30 mg/m^2 and 2 Gray TBI (Fig. 1). All donors were 9/10 or 10/10 HLA matched sibling or unrelated donors. Anti-thymocyte globulin (ATG) (2 mg/kg, during 4 consecutive days) was added when the donor was a (9/10) mismatched unrelated donor. Post grafting immunosuppression consisted of mycophenolate mofetil and cyclosporine. If patients had measurable residual disease (MRD) at start of the conditioning regimen, a bone marrow examination was repeated at day -1 or day 0 (= day of transplant) to define the MRD status directly after the decitabine treatment, before allografting. MRD was assessed with flow cytometry and was defined positive if the leukemia associated phenotype was >0.1%, as defined by the ELN MRD working party [15]. At day +21, +40, + 180, +365 after allo HCT and at relapse the following data were collected: bone marrow evaluation, donor T cell chimerism (assessed on whole peripheral blood using real time PCR with allele-specific primers for DNA-sequences containing single nucleotide polymorphisms (SNPs)), laboratory results, adverse events, survival status, and the occurrence of graft-versus-host disease (GVHD). Successful engraftment was defined according to European Bone Marrow Transplant (EBMT) criteria of hematopoietic repopulation [16]. Acute GVHD (aGVHD) was graded according to the criteria of Harris et al. [17] and chronic GVHD (cGVHD) was classified according to the NIH scoring system [18]. Safety endpoints were scored according to CTCAE 4.0. In case patients had a transplant rejection they went off-study.

Day	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
Decitabine 20mg/m^2	1	2	3	4	5	6	7	8	9	10		
Fludarabine 30mg/m^2								1	2	3		
TBI[1] 2 gray											x	
Stem cell infusion												x

Fig. 1 The DEC/FLU/TBI regimen. At day -11, decitabine (DEC) was started for 10 days, followed by fludarabine (FLU) at day -4 for 3 days and total body irradiation (TBI) 2 gray at day -1. At day 0, the stem cells were infused. In case a mismatched unrelated donor was used, also anti-thymocyte globulin (ATG) 2 mg/kg was added at day -8 for 4 consecutive days.

Endpoints

Primary study endpoint was cumulative 1-year relapse incidence. Relapse following CR is defined as reappearance of blasts in the blood or the finding of more than 5% blasts in the bone marrow (BM), not attributable to another cause.

Secondary endpoints were NRM, OS and relapse-free and GVHD-free survival (GRFS). NRM, relapse-free survival (RFS), and OS were defined according to ELN criteria [19]. GRFS was defined as surviving the first 12 months after allo HCT without relapse and without grade III-IV aGVHD and/or severe cGVHD [20].

Statistics

Historically relapse rate is about 55% in poor and very poor risk subgroups after allo HCT. Among others Cornelissen et al. report 43% relapse at 5 year in unfavorable karyotype patients and 68% in monosomal karyotype patients [1]. We hypothesized that the relapse rate would decrease from about 55% to 27% (Hazard ratio (HR) 0.5) by adding decitabine to the standard Flu/TBI schedule. Based on our preliminary data we found it justified to aim for a 1-sided alfa of 5% and we assumed a NRM of 15%. In the perspective of these assumptions we calculated, using a'Hern's Single Stage Phase II design, that 45 patients need to be included to demonstrate a decrease in relapse (at 1 year) of 55% to 33% (HR 0.6).

Descriptive statistics were used to characterize the cohort. A competing risk analysis was performed to obtain relapse incidence estimates with death and rejection as a competing risk. The Kaplan-Meier statistics was used to obtain estimates for OS, RFS, and GRFS. A p value smaller than 0.05 was considered statistically significant. Analyses were done with SAS ® 9.4 and IBM SPSS Statistics 25.

This study was carried out in The Netherlands and Belgium in accordance with the applicable rules concerning the review of research ethics committees and informed consent. The trial was registered at www.clinicaltrials.gov (NCT02252107).

Results

Patient and disease characteristics

Forty-six patients with a median age of 60 years (range 23–74) were included between 2014 and 2018. A summary of the patient and disease characteristics is shown in Table 1. Three patients received a mismatched allograft and therefore received ATG (8 mg/kg) in their conditioning, all other patients received DEC/Flu/TBI without ATG. Seventeen AML patients (37%) were classified as poor and 29 patients (63%) as very poor risk AML according to the HOVON-132 risk classification. Of all patients, 29 patients (63%) did not have a CR after 1 cycle of intensive induction chemotherapy, 7 patients (15%) had a WBC $> 100 \times 10^9$/L at diagnosis, and 31 patients (67%) had an abnormal karyotype or molecular mutations, of whom 6 patients (13%) a monosomal karyotype and 9 patients (20%) a complex abnormal karyotype. Twenty-nine patients (63%) had 2 or more of these high risk features. According to the later defined European LeukemiaNET (ELN) 2017 criteria for defining the cytogenetic/molecular risk in AML [19], we reclassified patients according to the ELN2017 criteria. Twenty-nine patients (63%) were classified as adverse risk, 14 patients (30%) as intermediate, and 3 patients (7%) as favorable risk. All 3 ELN favorable patients that were included in this protocol as 'poor risk' patients had a NPM1 mutation with/or without a (low allelic burden, ratio < 0.5) FLT-3 ITD mutation. They were eligible because they were > 60 years of age ($n = 2$), had not achieved an early CR ($n = 2$) and presented with hyperleukocytosis ($n = 2$).

Outcome

Median follow up was 44 months (range 31–65 months). Eleven patients (23%) had a relapse within the first year after allo HCT (see Fig. 2a–c). In total, 13 patients relapsed. Median time until relapse was 130 days (range 3–592). Eight out of these 13 patients (62%) had very poor risk disease. One of the relapsed patients received ATG pre

Table 1 Patient characteristics.

$N = 46$	n (%)	ELN adverse risk $N = 29$	ELN no adverse risk $N = 17$
Age			
Median (range)	60 (23–74)	60 (23–74)	62 (29–71)
≥60 years	24 (52)	15 (52)	9 (53)
Male	24 (52)	16 (55)	8 (47)
Type of disease			
De novo AML	41 (89)	27 (93)	14 (82)
Secondary AML	5 (11)	2 (7)	3 (18)
WHO classification 2008			
AML with recurrent genetic abnormalities	4 (9)	4 (14)	0 (0)
AML with myelodysplasia related changes	15 (32)	10 (35)	5 (29)
Therapy-related myeloid neoplasms	4 (9)	3 (10)	1 (6)
AML, not otherwise specified	22 (48)	12 (41)	10 (59)
Myeloid sarcoma	1 (2)	0 (0)	1 (6)
Disease status at start of conditioning			
Complete remission (CR)	29 (63)	20 (69)	9 (53)
Incomplete remission (CRi)	17 (37)	9 (31)	8 (47)
Median days between diagnosis and CR1 (range)	48 (25–147)	47 (25–147)	49 (27–103)
Median days between diagnosis and SCT (range)	116 (54–190)	115 (54–190)	121 (90–163)
MRD[a] status pre decitabine			
Negative	30 (65)	17 (59)	13 (77)
Positive	14 (31)	10 (34)	4 (23)
Missing	2(4)	2 (7)	0 (0)
MRD[a] after 10 days of decitabine at $t = 0$			
Negative	37 (81)	20 (69)	17 (100)
Positive	2 (4)	2 (7)	0 (0)
Unknown	7 (15)	7 (24)	0 (0)
Extra medullar disease			
Yes	2 (4)	0 (0)	2 (12)
Sorror co-morbidity index (HCT-CI)			
Median (range)	2 (0–8)	2 (0–8)	1 (0–6)
≤2	29 (63)	19 (66)	10 (59)
≥3	17 (37)	10 (34)	7 (41)
EBMT risk score (Grathwohl score)			
Median (range)	2 (0–4)	2 (0–4)	2 (1–4)
≤2	31 (67)	18 (62)	13 (77)
≥3	15 (33)	11 (38)	4 (23)
Donor type			
Matched 10/10			
SIB[b]	16 (35)	12 (41)	4 (24)
MUD[c]	27 (59)	17 (59)	10 (59)
Mismatched 9/10			
MMUD[d]	3 (6)	0 (0)	3 (17)
Median donor age (range)	32 (19–66)	32 (21–66)	32 (19–63)
Donor sex			
male	25 (54)	15 (52)	10 (59)
CMV positive donor			
CMV neg patient	8 (18)	5 (17)	3 (18)
CMV pos patient	14 (30)	9 (31)	5 (29)
CMV negative donor			
CMV neg patient	14 (30)	6 (21)	8 (47)
CMV pos patient	10 (22)	9 (31)	1 (6)
EBV positive donor			
EBV neg patient	5 (11)	2 (7)	3 (18)
EBV pos patient	38 (83)	25 (86)	13 (76)
EBV negative donor			
EBV neg patient	0 (0)	0 (0)	0 (0)
EBV pos patient	3 (6)	2 (7)	1 (6)
Stem cell source (%)			
Peripheral blood	44 (96)	27 (93)	17 (100)

[a]MRD = minimal residual disease.

[b]SIB = sibling donor.

[c]MUD = matched unrelated donor.

[d]MMUD mismatched unrelated donor.

allografting. Of the 29 patients with adverse risk according to ELN 2017 criteria, 9 patients (31%) developed a relapse. Seventeen patients were in CRi at start of conditioning, and 6 (35%) of these patients had a relapse, versus 6 (21%) of the 29 patients that were in CR. NRM was 5% within the first 100 days post HCT, and 11% within the first year post allo HCT. One-year OS, RFS, and GRFS were 70%, 66%, and 45% respectively (see Fig. 3a). After 4 year this was 56%, 52% and 26% respectively. One-year OS in poor and very poor risk patients according to HOVON-132 criteria was 88% and 59% respectively. When the ELN-2017 criteria were applied on this cohort, the one-year OS for the adverse risk was 55% and the one-year OS for the non-adverse group was 94%. (see Fig. 3b, c). During the follow-up, 18 patients died, 11 due to relapse, 3 due to GVHD, 2 due to infection, 1 due to heart failure and 1 due to suicide.

MRD conversion

Fourteen patients (30%) were MRD positive at the start of conditioning, and in 10 of these patients the MRD status was repeated at day -1/day 0. Seven of them became MRD negative. None of these 7 patients, who became MRD-, developed a relapse during the follow up of the study. The 1 year OS for MRD+ and MRD- patients (as measured at $t =$ 0, allo HCT) was respectively 50% and 74%.

Transplant related complications and adverse events

The in-hospital stay during conditioning/allografting had a median duration of 19 days (range 1–72). Twenty-four (52%) and 37 (80%) patients had full engraftment before day 21 and day 40 respectively. Rejection was seen in 3 patients (7%) at day 40, day 52 and day 117, respectively.

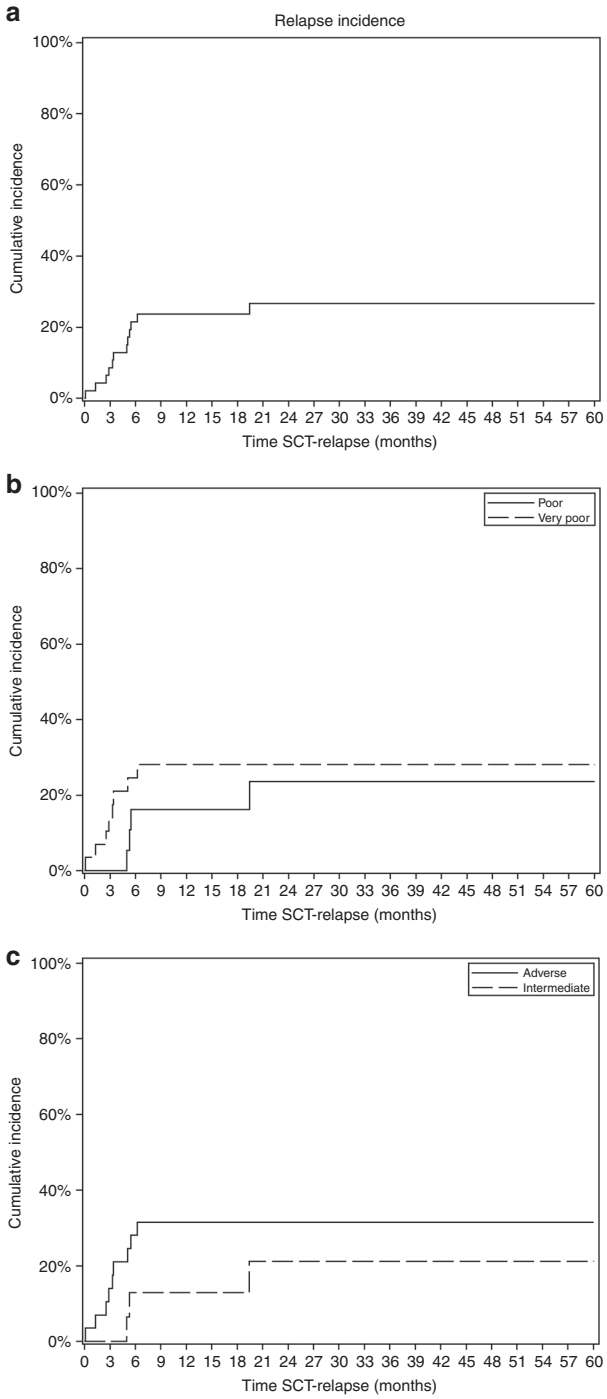

Fig. 2 Incidence of AML relapse during follow up. a Relapse incidence for all patients, $n = 46$. **b** Relapse incidence in patients with poor (solid line) and very poor (dashed line) risk disease, as defined in the method section. **c** Relapse incidence in patients with adverse (solid line) and intermediate (dashed line) risk AML, as defined by the ELN 2017 criteria.

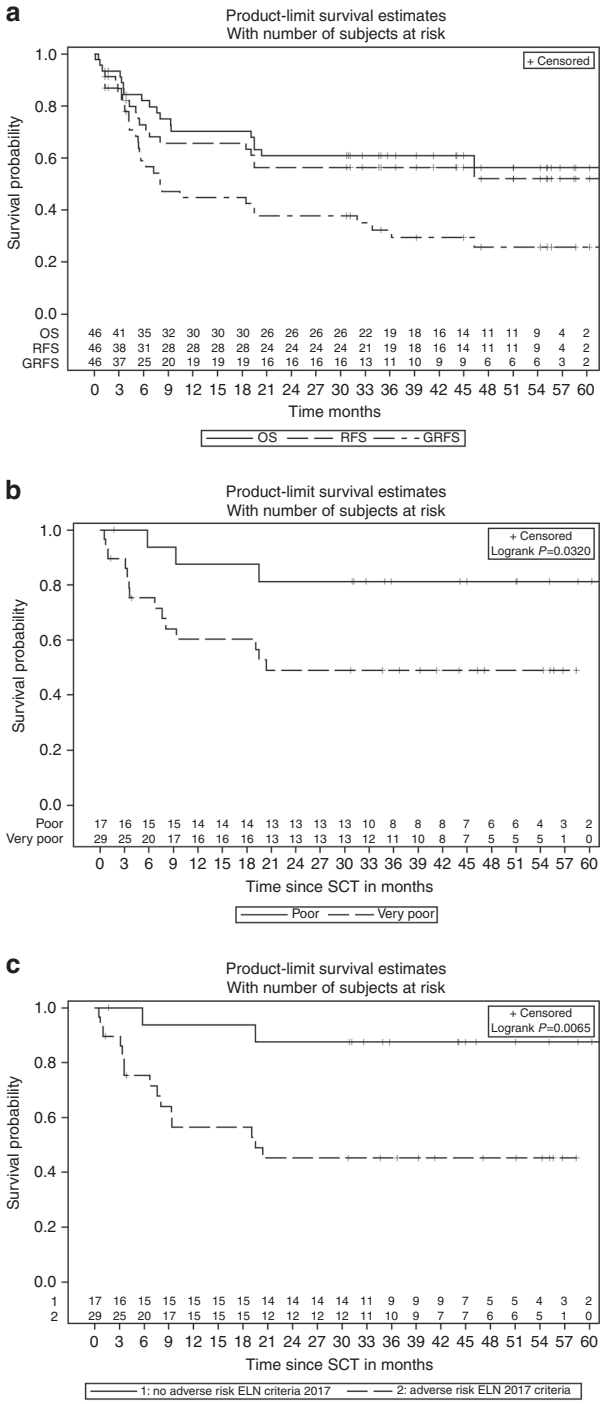

Fig. 3 Overall survival (OS), relapse-free survival (RFS), and graft-vs-host-free and relapse-free survival (GRFS). a OS, RFS, and GRFS for all patients. **b** OS for patients with poor (solid line) and very poor (dashed line) risk AML. **c** OS for patients with adverse risk (dashed line) and no-adverse (solid line) risk AML according to the ELN 2017 criteria.

Of these 3 patients 2 had received bone marrow stem cells from a matched donor and 1 patient had received peripheral blood stem cells from a matched donor. Twenty patients (44%) developed aGVHD gr I-IV after a median of 53 days (range 12–350). Grade III-IV aGVHD was seen in 6 patients (13%), and 2 of them eventually died due to aGVHD. Twenty-three (50%) patients developed any grade of cGVHD, and this was graded as severe in 9 (20%) of them, in one of them this was fatal. Grade 3–4 adverse

events that were seen in >5% of patients were febrile neutropenia (9%) and other infections (9%).

Discussion

In this phase II intervention study a 10-day decitabine regimen was added to the standard NMA conditioning (DEC/FLU/TBI) before allografting in poor risk AML patients already in CR/CRi, with the hypothesis that deepening of remission before allografting and immune modulation of remaining disease would reduce relapse rate. We observed an AML relapse rate of 23% and a NRM of 11% in the first year after allo HCT. The 1-year OS, RFS, and GRFS were 70%, 66% and 45% respectively.

Former studies reported relapse rates of 40–68% in poor risk AML patients and OS of 29–54% and 22–40% after MAC and NMA allo HCT respectively [1, 2, 5, 6]. In our study population with a mature median follow up of 44 months, the 4-year OS was 56% after NMA conditioning. The comparison with other studies on poor risk AML is not straightforward, due to the use of different risk criteria. In addition, NMA and MAC regimens are often compared in a retrospective manner. This could lead to selection bias, since older AML patients more often undergo NMA allo HCT compared to younger patients [5, 7]. After the introduction of the new ELN 2017 risk classification criteria we redefined our patients according to ELN risk, and found that the poor and very poor risk groups corresponded well with the ELN intermediate and adverse risk group respectively, overlapping in 83% of cases. Applying the ELN risk criteria on our study cohort, 1-year relapse rate was still low in the adverse risk group (31%), with a 1-year OS of 56% and a 4-year OS of 45%. To compare, a retrospective study of Yanada et al. found a 1-year relapse rate of >40% in poor risk patients, and a 1-year OS of nearly 50% with MAC and 30% with NMA conditioning [2]. In this light our results seem encouraging as an alternative approach. Also in younger patients with poor risk disease, it could be argued whether our new regimen would be preferable. A study by Konuma et al. with patients with high risk disease found a better OS after MAC conditioning compared to NMA conditioning (3-year OS MAC 54%/RIC 40%), although this effect was only seen in patients younger than 60 years of age and in cytogenetic negative CR [6]. Gilleece et al., concluded as well that NMA HCT was inferior to MAC, although only in the MRD positive patients under the age of 50 [9]. So, the impact of MRD is evident, although the impact of MAC to improve outcome in these patients seems unclear.

In our cohort, when comparing MRD status pre- and post decitabine conditioning, we found that 7 of 10 MRD positive patients became MRD negative directly after 10 days of decitabine. It would be interesting to investigate in a larger cohort if the addition of decitabine can indeed increase the number of patients that become MRD negative prior to allografting and if this could explain our lower rate of relapses and improved survival. In a previously study, we showed that the use of decitabine with NMA conditioning improves the amount of CD8 positive T cells against TAAs [13], which is an interesting example of one of the immunologic actions of HMA. In the past it had been shown that HMAs can increase the expression of these epigenetically silenced TAA on tumor cells and also of minor histocompatibility antigens (MiHAs) [14, 21]. We think that the residual tumor cells after decitabine treatment, with increased TAA and MiHA expression, can eventually lead to presentation of these peptides by antigen-presenting cells, and evoke an donor-derived T cell response against these antigens. This might lead to increased immune clearance of leukemic blasts and could provide an explanation for the lower relapse rates observed.

Furthermore, we showed that the addition of decitabine did not increase NRM (1-year NRM 11%), compared to standard NMA conditionings [3, 4]. This is also an important finding, since many of our patients cannot tolerate a more toxic regimen, especially in older patients or patients with comorbidities. Recently D'angelo et al. [22] concluded that they found a high risk of infection (55% grade 3–4 infections) and mortality (25% survival after a median follow up of 3.6 years) after decitabine induction, however, in their protocol patients received decitabine 17–24 days before start MAC conditioning, with all patients becoming neutropenic after decitabine. We started the conditioning with 10 days of decitabine and directly continued with a NMA regimen. So, the duration of neutropenia was shorter in our patients, and also antibiotic prophylaxis was given during this period. This might explain the low NRM in our cohort as well as the lower amount of severe infections (9% grade 3–4 infections and 9% febrile neutropenia).

A limitation of our study is the relatively low number of patients we included, although this was based on a power calculation to demonstrate a relapse reduction (of 55% to 33%; HR 0.6) after 1 year compared to historical results. Unfortunately we cannot extract patients of 60 years or older for a meaningful sub-analysis and compare this subgroup with former research on poor risk disease in older patients that received NMA HCT.

In summary, in this prospective phase 2 study we found that addition of 10-day decitabine to NMA conditioning seems to be a safe strategy that might add to lower relapse rates in patients with poor or very poor risk AML who receive an allo HCT. Future research is necessary to confirm if this schedule indeed can decrease relapse, especially in elderly poor risk AML patients, and in those with MRD positive disease prior to conditioning.

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Compliance with ethical standards

Conflict of interest GH joined advisory boards of Celgene and Jansen.

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