Fractionated gemtuzumab ozogamicin in association with high dose chemotherapy: a bridge to allogeneic stem cell transplantation in refractory and relapsed acute myeloid leukemia

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Fractionated Gemtuzumab Ozogamicin in association with high dose Chemotherapy: a Bridge to Allogeneic stem cell Transplantation in Refractory and Relapsed Acute Myeloid Leukemia

Running Head: Gemtuzumab and chemotherapy in acute myeloid leukemia

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Abstract:

Optimization of the salvage regimen is required to improve prognosis in primary refractory or relapsed acute myeloid leukemia (AML). In fit patients, a bridge to allogeneic transplant is the primary purpose of salvage. We tested the combination of fractionated gemtuzumab ozogamicin with cytarabine and mitoxantrone (MYLODAM schema) with primary endpoint of efficacy and safety. We also attempted to define predictive factors for survival and response after salvage.

We included 58 patients with a median age at salvage of 56 years. The overall response rate was 67%. Leukemia-free survival (LFS) and overall survival (OS) at 2 years was 36% (95% CI: 23 - 49) and 54% (95% CI: 39 - 68), respectively. Treatment-related mortality was 7%. Three veno-occlusive diseases (SOS/VOD) occurred during salvage. In the allogeneic group of 28 patients (48%), LFS and OS at 2 years was 57 % (95% CI: 36.3 - 77.5) and 69 % (95% CI: 49.3 - 88.7), respectively. Incidences of non-relapse mortality, grade II-IV acute graft-versus-host disease (GVHD) and chronic GVHD were 16%, 40%, and 45%, respectively.

A GO-based intensive regimen is a viable option for salvage therapy and a feasible schedule as a bridge to allogeneic transplant.

Introduction

Despite the improvement in care, primary refractory or relapsed acute myeloid leukemia (PR-AML) is associated with a dismal prognosis. Approximately one-third of patients younger than 60 years and 50% of older patients with newly diagnosed AML fail to achieve complete remission (CR) after first line intensive chemotherapy.[1–3] Furthermore, nearly 40% of patients initially achieving first complete remission (CR1) experience relapse[4], and the median duration of a second CR is often shorter than that of CR1. Refractory AML (20% of patients) is a major unfavorable prognostic factor with a median survival of 12 months.[5] Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the only salvage option with curative potential in these two scenarios.[6] However, disease status at transplant remains one of the

main prognostic factors.[7,8] There is no consensus on the optimum salvage therapy which may be used as a bridge to allo-HCT.[9,10] Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 antibody conjugated with the cytotoxic antitumor antibiotic calicheamicin. GO (6 or 9 mg/m² during one day) first received accelerated approval in 2000 for treatment of CD33-positive AML in patients aged ≥60 years of age who experienced disease relapse and were not considered candidates for cytotoxic chemotherapy. However, myelosuppression, fatal hepatotoxicity, and high risk of sinusoidal obstructive disease/veno-occlusive disease (SOS/VOD) were reported in the post-marketing setting. Finally, the confirmatory study, S02106, failed to demonstrate a clinical benefit for GO.[11] A UK National Cancer Research Institute meta-analysis of 5 phase 3 trials of GO in adults studied 3.325 patients.[12] This meta-analysis showed a statistically significant reduction in relapse rates and improved overall survival (OS) for GO-treated patients across these trials, without a significant increase in toxicity. The benefits appeared to be limited to patients with a favorable or intermediate-risk karyotype; patients treated on studies with 3 mg/m² per dose or with a fractionated schedule of 3 mg/m² on day 1,4 and 7, experienced lower induction mortality. In light of this more favorable reassessment of randomized studies, GO was given full FDA approval in September 2017 for treatment of CD33-positive AML, both in the frontline and relapse setting. In the PR-AML setting, MIDAM protocol (GO 9 mg/m² on day 4, cytarabine 1 g/m² twice daily on day 1-5 and mitoxantrone 12 mg/m² on day 1-3) has an overall response rate (defined as CR+CRi (same as CR except for one criterion of peripheral blood count recovery) of 63%.[13] In a phase 2 study of PR-AML, GO monotherapy demonstrated efficacy with an overall response rate (CR+CRi) of 33% and no grade 3–4 liver toxicity.[14]

Based on the preceding results, we tested the combination of the fractionated GO (3 mg/m² on day 1, 4 and 7) with intensive chemotherapy, namely cytarabine (1 g/m² twice daily on day 1-

5) and mitoxantrone (12 mg/m² on day 1-3). This combination, namely MYLODAM, became a first salvage therapy for PR-AML at our center.

This single-center retrospective analysis aimed to assess the outcomes of PR-AML patients treated with this regimen.

Patients and Methods

Patients

This study included consecutive patients, potentially eligible for allo-HCT, treated in our institution that had either refractory or relapsed AML. Refractory AML was defined as failure to achieve a morphological CR in the bone marrow after one induction chemotherapy. Relapsed AML was defined by >5% blast in the bone marrow after CR. The CD33 expression level was determined by dividing the mean fluorescence intensity of CD33 of the leukemic blast cells by the mean fluorescence intensity of the isotypic control. The threshold for positivity was defined as a ratio of ≥ 2.

Detection of mutations FLT3-ITD, NPM1, and CEBPA was performed with standard routine techniques.[15]

Cytogenetic analysis was performed on R-banding metaphases after 24-hour culture using standard procedures. Chromosomal rearrangements were confirmed by fluorescent *in situ* hybridization (FISH) analysis on 200 interphase nuclei. FISH was performed in CR samples (200–400 nuclei) to evaluate the clearance of chromosomal abnormalities with a theoretical detection threshold of 0.5%.

Sequencing was performed using a 122 gene panel (HaloPlex Target Enrichment System®, Agilent Technologies) on a MiSeq® sequencer (IlluminaINC). Detailed protocols have been reported previously.[16] After alignment, described variants were called using an Ensembl

database. Non-described variants of potential interest were also sequenced using the Sanger method in the CD3+ fraction or the CR samples.

Salvage regimen

MYLODAM involved GO 3 mg/m² (maximum dose 5 mg) on days 1, 4, and 7 with different chemotherapies. These mainly consisted of cytarabine (1 g/m² twice daily on day 1-5) and an antracycline (either daunorubicin 60 mg/m² or idarubicine 12 mg/m² on day 1-3 or mitoxantrone 12 mg/m² on day 1-3). In the case of CR, some patients received consolidation therapy with GO at 3 mg/m² (maximum dose of 5 mg) on day 1 associated with chemotherapy (described in results). Patients who were fit for allo-HCT received an allogeneic graft if a donor was available after salvage or after consolidation.

Response criteria

Response to salvage therapy was evaluated by bone marrow studies which were performed earlier in the case of suspected disease progression. Complete remission (CR) was defined as normalization of blood and bone marrow: $\leq$ 5% of blasts, neutrophil count >1.5 G/L, and platelet count >100 G/L. CRi was defined as CR, except for one criterion of peripheral blood count recovery. CRMRD- was defined as CR with negative MRD by flow cytometry or molecular target. Overall response (OR) was defined as CR + CRi + CRMRD-. The European Leukemia Net (ELN) 2017 classification was used for prognostic classification and definition of response.[17]

The WHO Toxicity Grading Scale was used to characterize toxicity. Evaluation of SOS/VOD was defined according to the grading system from the European Society for Blood and Marrow Transplantation.[18]

The primary endpoints in this analysis were the efficacy and safety profile of the MYLODAM salvage strategy. We also attempted to define predictive factors for survival and response after

salvage. The following prognostic factors were recorded: age, cytogenetics, molecular data, blood cell counts, Sorror score[19], and duration of CR1. We also recorded outcomes and safety data following allo-HCT.

Statistical analysis

Overall survival (OS) was calculated from the date of the start of therapy until death. LFS was calculated from the date of the start of therapy to disease recurrence or death.

Neutrophils recovery was determined as the interval from the therapy start to the first of 3 consecutive days with an absolute neutrophil above 0.5 G/L. Platelets recovery was determined as the interval from therapy start to the first of 7 consecutive days with a platelet above 20 G/L without transfusion.

Acute GVHD (aGVHD) was graded according to Glucksberg classification[20]. Chronic GVHD (cGVHD) was diagnosed using the NIH classification[21]. Non-relapse mortality (NRM) was calculated from the date of HSCT to death not related to disease recurrence.

Cumulative incidence, treating non-event deaths as a competing risk, was used to estimate the probability of relapse, NRM, and acute and chronic GVHD. Kaplan – Meier curves were plotted for survival, and data for the various groups were compared using the log-rank test. Multivariate analysis was performed with a Cox model after the proportional hazards assumption was checked. Only significant univariate variables ($p<0.1$) were included. A p-value of less than 0.05 was considered statistically significant. 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. https://www.R-project.org/.) »

Results

Patients' characteristics

Fifty-eight patients (38 relapses and 20 primary refractory at chemotherapy) were included from 2009 to 2017 (Table 1). The median age at salvage was 56 years (range 16-74). Seventy-four percent were de novo AML (n=43) and 26% secondary AML following myelodysplastic syndrome (n=7) or therapy-related (n=8). Eight patients (16%) had a WHO classification-based performance status (PS) >1 at salvage (missing data, n=9). Based on the ELN 2017 classification, the prognosis was favorable for 23 patients (40%), intermediate for 21 patients (36%) and adverse for 14 patients (24%). Also, 46 patients (79%) had minimal residual disease (MRD) target. All patients had CD33 positive AML (cut-off 20%) with a median of 85% of expression (range 28-100%). Bone marrow median blast count at the time of salvage treatment was 23 % (range 0-94). Three molecular and 1 phenotypic relapse were treated.

Thirty-six (62%) patients received fractionated GO with cytarabine (1 g/m² twice daily) and mitoxantrone (12 mg/m² on day 1, 2 and 3). Fourteen patients (24%) had fractionated GO combined with cytarabine (1 g/m² twice daily on day 1-5) and daunorubicin (60 mg/m² on day 1, 2 and 3). Seven patients (12%) received fractionated GO combined with cytarabine (1 g/m² twice daily on day 1-5) and one (2%) received fractionated GO combined with cytarabine (1 g/m² twice daily on day 1-5) and idarubicin (12 mg/m² on day 1, 2 and 3).

Response

The median follow-up period of alive patients was 26 months (range 2 - 84). The overall response rate was 67% (17% CRi, 17% CR, and 33% CRMRD-). After first cycle of MYLODAM, MRD negativity was achieved in 41% of patients with MRD target which included 8% with CRi and MRD-. Two predictive factors were associated with a lower response rate: refractory disease and male gender (Table 2). The median LFS and OS of all patients were 13.5 months (range 6-21) and 50 months (range 11-90), respectively (Figures 1

and 2). LFS and OS at 2 years was 36% (95%CI 23-49) and 54% (95%CI 39 - 68), respectively. Description of patients treatment and outcomes after MYLODAM was presented in figure 3. The overall response rate in patients with prior allo-HCT was 84% with 6 patients which could proceed to second allo-HCT. Five patients died in patients with prior allo-HCT. In relapse AML, longer duration of CR1 was associated with LFS (p=0.03). In the multivariate analysis, LFS was significantly correlated with ELN prognostic score, with a lower LFS in the adverse risk group (HR=2.47; 95%CI: 1.05-5.79. p=0.038) and with differentiation mutation (HR=3.53, 95%CI 1.54-8.08; p=0.003). At 2 years, relapse incidence (RI) was 62% and multivariate analysis demonstrated that both an adverse ELN score and differentiation mutations were associated with a higher RI (HR=2.67, 95% CI: 1.17-6.38, p=0.027; HR=3.61, 95% CI: 1.56-8.35, p=0.003), respectively.

Toxicity

The median duration of hospitalization was 42 days (range, 22-133). Main toxicities are reported in Table 3. Cumulative incidences of neutrophils and platelets recovery at day 60 were 80 % (95%CI 67-89) and 91 % (95%CI 78-96), respectively. Three patients developed SOS/VOD without prophylaxis during the MYLODAM salvage therapy, 2 with moderate and 1 with very severe grade. Concerning infections, 57% were due to bacteriemia (13 enterobacteria, 10 *Staphylococcus* sp, 7 *Enterococcus* sp, 5 *Pseudomonas* sp, 4 *Clostridium difficile*, 1 *Stenotrophomonas maltophila*, and 1 *Lactobacillus* sp). Despite posaconazole prophylaxis in most patients, we observed 5 cases of aspergillosis (10%) and 1 candidiasis (2%). One pneumocystis occurred during salvage. Four patients required admission to ICU for sepsis (n=2), hemorrhagic events (n=1) and neurologic dysfunction (n=1). Therapy-related mortality was 4 patients (7%): 2 from infection, 1 from a hemorrhagic event, and 1 from very severe SOS/VOD.

Subsequent treatment

Nineteen patients received consolidation treatment after CRi/CR/CRMRD. Protocols were GO at 3 mg/m² on day 1 (8 patients); GO at 3 mg/m² on day 1 associated with cytarabine 1 g/m² twice daily on day 1-4 (8 patients); GO at 3 mg/m² on day 1 associated with cytarabine 1 g/m² twice daily on day 1-4 and mitoxantrone at 12 mg/m² on day 1- 2 (3 patients). Nine of these 19 also received a second consolidation. Protocols were GO at 3 mg/m² on day 1 (3 patients); GO at 3 mg/m² on day 1 associated with cytarabine 1 g/m² twice daily on day 1-4 (4 patients); GO at 3 mg/m² on day 1 associated with cytarabine 1 g/m² twice daily on day 1-4 and mitoxantrone at 12 mg/m² on day 1-2 (2 patients). Three patients had an improvement in response with 2 patients in CR moving to CRMRD- and one patient in CRi moving to CR. Two patients experienced relapse during consolidation. No SOS/VOD occurred during consolidation courses. Two patients required ICU admission for sepsis.

In the non-allo-HCT group (n=30), LFS and OS at 2 years was 26 % (range 14.7-50) and 33 % (range 22-61) respectively. Eighteen patients out of 30 experienced disease relapse that was treated with azacitidine (n=7), cytarabine (n=4), arsenic trioxide + All-Trans Retinoic Acid (ATRA) (n=1) and best supportive care (n=6). Refractory AML was the leading cause of death (n=17).

Allogeneic transplant group

In all, 28 (48%) patients could proceed to allo-HCT. The median time between treatment by MYLODAM and allo-HCT was 91 days (range 57-366 days). The main reason to exclude allo-HCT for the 30 other patients was that 19 were not fit enough after salvage treatment, 6 died before transplant, and for 5 patients no donor could be identified. The Sorror score for the transplant patients was calculated as 0 for 11 patients, 1 for 5 patients, 2 for 7 patients, and

3 for 5 patients respectively. Stem cell sources were peripheral blood stem cells in 22 patients, bone marrow in 4 patients, and umbilical cord blood in 2 patients.

LFS and OS at 2 years was 57% (range, 36.3-77.5) and 69% (range, 49.3-88.7) respectively (Table 4). The cumulative incidences of grade II-IV acute GVHD and chronic GVHD were 40% and 46%, respectively. At 2 years, the cumulative incidence of NRM was 16 % (95% CI: 8.5-33.3), and of RI was 25 % (95% CI: 10.5-46.8).

Despite the policy of our center to prevent SOS/VOD in this high-risk patient group by using defibrotide prophylaxis (21 out of 28 patients received prophylaxis), 5 cases of SOS/VOD occurred during allogenic transplant (3 moderate and 2 very severe). All 5 cases received TEC-RIC conditioning for allo-HCT in the 3 months after MYLODAM, defibrotide prophylaxis. However, no death related to SOS/VOD was observed.

Prophylactic donor lymphocyte infusions (DLIs) were administered to 4 patients. In the post-transplant setting, 5-azacitidine was administered to 8 patients: 4 patients in prophylaxis, 2 in preemptive treatment (MRD+), and 2 in relapse.

Cytogenetics, molecular and Next Generation Sequencing (NGS) description

Based on the classification of ELN 2017, 23 patients had a favorable prognosis, 21 had an intermediate prognostic, and 14 had an adverse prognostic. In terms of cytogenetics, 28 presented with a normal karyotype, 4 with monosomy 7, 3 with abnormalities in chromosome 3, and 3 with t(v;11q23.3).

Forty-seven patients were able to have NGS analysis at diagnosis, and the profile of mutations is presented in Figure 4. The median number of mutations was 2 (range, 0-7), which did not have an impact on LFS and OS. We used a classification of mutations to determine prognosis with NPM1, FLT3 (FLT3-ITD, FLT3-TKD), CBF (inv(16), t(8;21)), methylation abnormalities (DNMT3A, TET2, IDH1, IDH2), signaling pathways (NRAS, KRAS, PTPN11,

CBL, NF1, CS3FR), differentiation abnormalities (RUNX1, GATA 2, inv(3), t(3;3)), chromatin abnormalities (ASXL1, t(v;11q23.3), MLL, EZH2, ASXL2, BCOR), spliceosome (SF3B1, SRSF2, ZRSF2) and cohesin (SMC1A, STAG2, RAD21). Multivariate analysis showed that differentiation abnormalities were associated with a significantly lower LFS (HR=3.53, 95% CI: 1.54-8.08, p=0.003) and a higher RI (HR=3.61, 95% CI: 1.56-8.35, p=0.003) (Table 2).

Discussion

This study shows that GO with chemotherapy in PR-AML is a very interesting salvage option for this high-risk group of patients. The overall response rate was achieved in 67% of patients, with OS and LFS rates of 54% and 36%, respectively. The safety profile was acceptable with 7% of TRM and 5% of SOS/VOD during salvage. Half of the patients could bridge to allo-HCT, albeit with 32% of patients not enough fit to proceed and a an increased risk of SOS/VOD (n=5, 18%) despite defibrotide prophylaxis.

These results seem to be superior or comparable to those observed with chemotherapy, GO as monotherapy, or GO plus chemotherapy. Indeed, studies using GO in combination with chemotherapy as a salvage regimen have shown a response rate of 38%-63%.[14,22–24] With the MIDAM protocol, Chevallier et al. evaluated 62 PR-AML patients, who received a combination of non-fractioned GO (9 mg/m²), cytarabine and mitoxantrone.[22] The overall response rate was 63% (50% CR and 13% CRi), and the 2-year OS and EFS were 41% and 33% respectively. Three percent of SOS/VOD was described with one death related to SOS/VOD. The combination of mitoxantrone and intermediate-dose cytarabine is known to be one of the most effective salvage regimens for PR refractory/relapsed-AML.[25] We used fractionated GO 3 mg/m^2 on days 1, 4, and 7 as in the trial ALFA-0701[26], as this schedule has been shown to be associated with a lower risk for early mortality and liver toxicity than the higher dose used in the failed SWOG S0106 trial.[11] Other chemotherapies (MEC, FLAG,

HIDAC, …) without GO in salvage regimen for AML offer 20-60% of ORR with nearly 10% of TRM.[27–29]

Identification of valid and reproducible biomarkers for response to GO is necessary. High-level expression of CD33 was associated with a good response rate in other studies[30], but our analysis did not confirm this association. Data suggest that in pediatric AML with the CC genotype on CD33, a substantial response to GO[31] is evident, but one study on adults did not confirm this association[32].

SOS/VOD could occur during salvage and allo-HCT when patients were exposed to GO. We want to warn about 17% incidence of SOS/VOD during allo-HCT in our study despite defibrotide prophylaxis, higher than what was reported in a retrospective study of the EBMT.[33]

Our multivariate results confirm the importance of the ELN prognostic classification in relapsed and refractory AML, but the study was underpowered to determine the impact of each mutation. The development of MRD detection by NGS would allow us to follow the majority of patients and increase our knowledge of response depth.[34]

Our study was limited by its retrospective nature and monocentric characteristics. We have also introduced a possible selection bias with the therapeutic decision of salvage therapy, consequently selecting fitter patients with fewer comorbidities.

Conclusion

In summary, we conclude that in a “real-life” setting, a GO-based intensive regimen can offer effective salvage to patients with refractory or relapsed AML, allowing achievement of response in two-thirds of the cases and a bridge to allogeneic transplant in half of them. In the future, we need to select patients according to molecular setting (NGS), biomarker of

chemotherapy, and GO sensibility and decrease global toxicity to perform more frequently HCT.

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Conflict of interest

M.M has received lecture honoraria from Pfizer whose product is discussed in this article.

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Figures 1 and 2. Leukemia-free survival [LFS] and overall survival [OS].

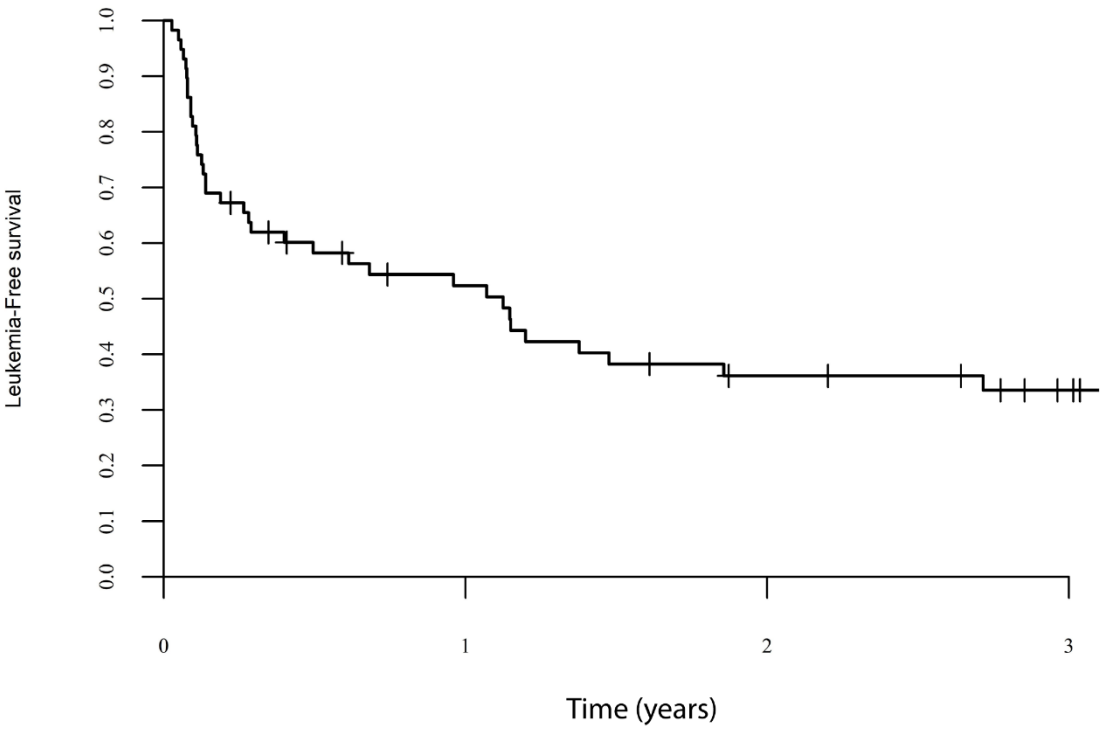

Fig 1. Leukemia-free survival curves

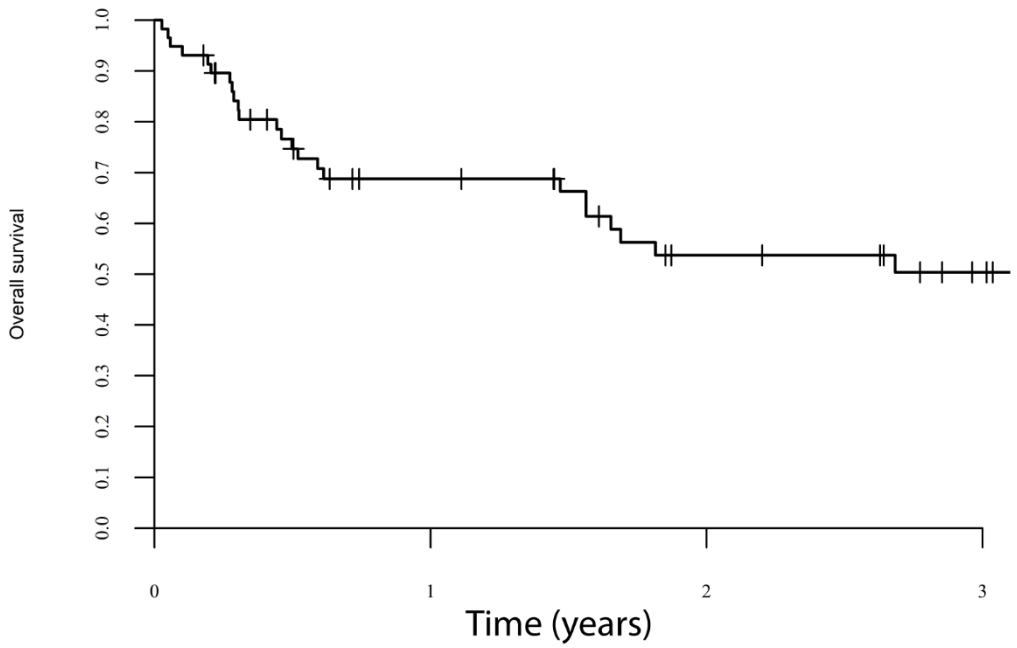

Fig 2. Overall Survival among All patients

Figure 3. Description of patients' outcomes after MYLODAM

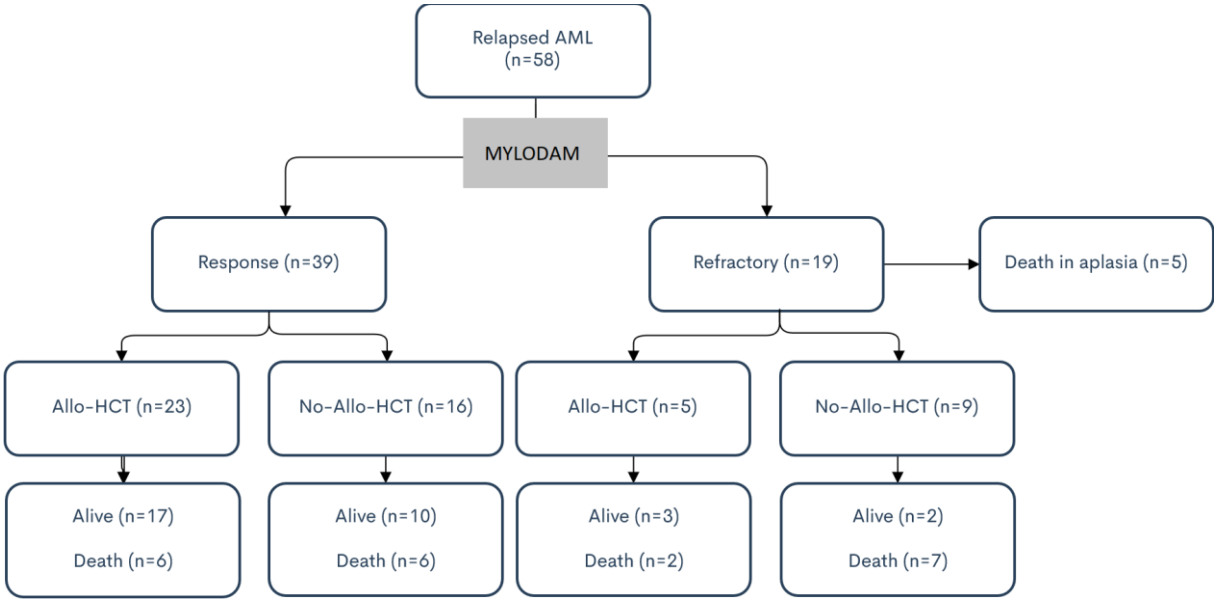

Figure 4. Description of mutation profile at diagnosis of AML.

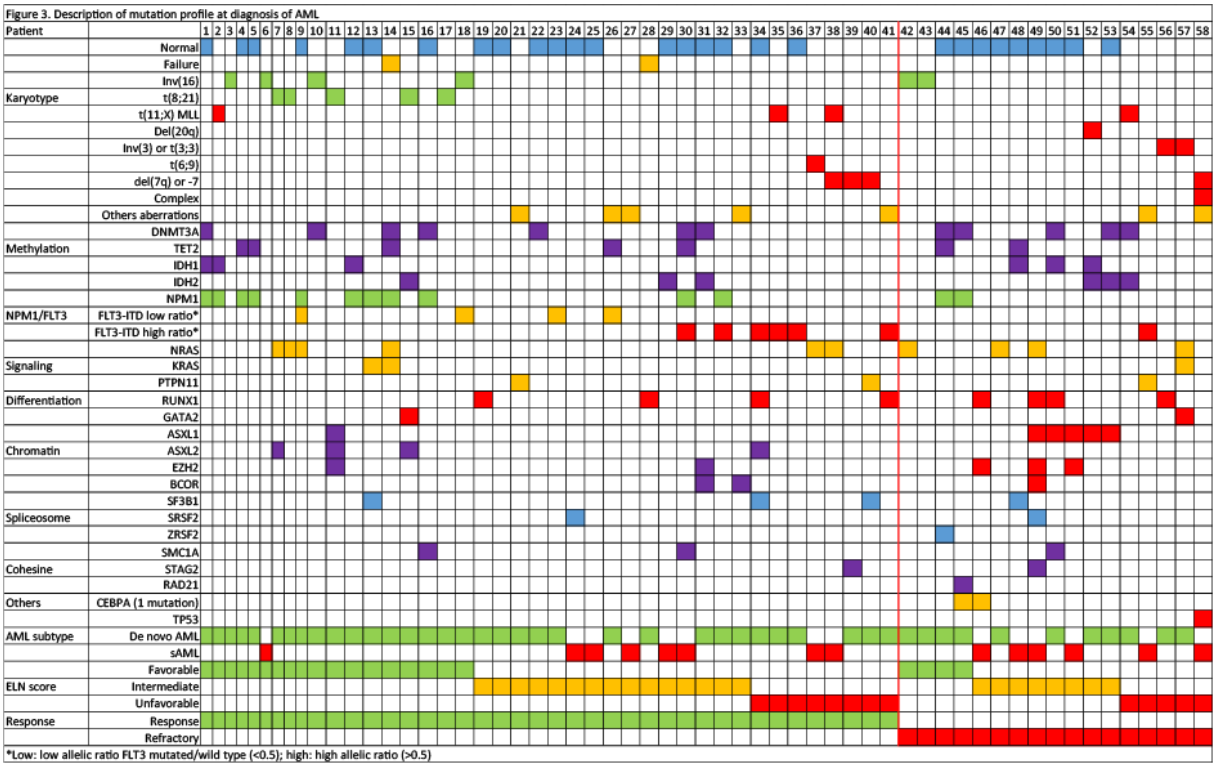

Table 1. Patient characteristics

Age at salvage treatment, years	
median (range)	56 (16-74)
< 60 y	33 (57%)
≥ 60 y	25 (43%)
Gender, n (%)	
Male	34 (59%)
Female	24 (41%)
Comorbidities, n	
HIV	2
Cardiac	3
Pulmonary	2
Renal	2
Liver	1
First-line therapy, n (%)	
Anthracycline + Cytarabine	46 (79%)
Anthracycline + Cytarabine + etoposide	8 (14%)
Others	4 (7%)
Status of disease at salvage, n (%)	
Relapsed	38 (66%)
Refractory	20 (34%)
Lines of treatment before salvage treatment, n (%)	
1	41 (71%)
2	7 (12%)
3	9 (15%)
4	1 (2%)
Prior allo-HCT	13 (22%)
CD33 expression, %	
Median	85
Range	28-100
ELN prognostic score, n (%)	
Favorable	23 (40%)
Intermediate	21 (36%)
Adverse	14 (24%)

Table 2. Multivariate analysis using the Cox proportional hazards model with backward stepwise selection. Only significant univariate variables (p<0.1) included.

		HR	p-value	95% CI	
				Lower	upper
Response	Refractory versus Relapse	3	**<0.01**	1.38	6.52
	Male versus Female	2.8	**<0.01**	1.33	5.93
	Mutations > 2	1.9	0.05	0.99	3.73
LFS	ELN favorable*				
	ELN intermediate	1.2	0.71	0.51	2.67
	ELN adverse	2.5	**0.04**	1.05	5.79
	Differentiation mutations	3.5	**<0.01**	1.54	8.09
	Chromatin mutations	2.1	0.06	0.97	4.56
OS	ELN favorable*				
	ELN intermediate	0.7	0.54	0.22	2.18
	ELN adverse	2.3	0.11	0.83	6.58
	Secondary leukemia	3.2	**0.01**	1.30	7.85
	Chromatin mutations	2.4	0.07	0.94	6.27
RI	ELN favorable*				
	ELN intermediate	1.3	0.58	0.55	2.96
	ELN adverse	2.7	**0.02**	1.12	6.38
	Differentiation mutations	3.6	**<0.01**	1.56	8.35
	Chromatin mutations	2.1	0.06	0.97	4.67
LFS: leukemia free survival, OS: overall survival, RI: relapse incidence, *reference group					

Table 3. Toxicity of MYLODAM

Toxicity (WHO grade)	Grade 1-2	Grade 3	Grade 4
Infections*	30	23	4
Hemorrhagic event	4	4	5
Cardiac dysfunction	2	0	1
Renal dysfunction	3	0	0
Elevated transaminases	30	9	6
GGT and alkaline phosphatase elavation	20	1	0
Hyperbilirubinemia	15	6	0

Table 4. Characteristics and outcomes of allo-HCT patients

	N = 28
Sex Ratio (M/F)	17 / 11
Median age, years (range)	48 (17-67)
> 60 years	6 (21%)
Conditioning regimen, n (%)	
MAC / RIC	7 (25%) / 21 (75%)
Donor Type, n (%)	
10/10 MRD	8 (29%)
10/10 MUD	7 (25%)
Haploidentical	11 (39%)
CBU	2 (7%)
Outcome 2 years after allo-HCT, % (95% Confidence interval)	
LFS	57 % (36.3 – 77.5)
OS	69 % (49.3 - 88.7)
RI	29%
NRM	16.1 % (8.5 - 33.3)
CI of acute GVHD II-IV at day 100	40 % (15.2 - 64)
CI of chronic GVHD	46 % (24.5 - 64.4)

Abbreviations : allo-HCT, allogeneic stem cell transplantation, M: male, F: female, MAC : myeloablative conditioning, RIC : reduced-intensity conditioning, MRD : matched related donor, MUD : matched unrelated donor, CBU : cord blood unit, LFS : leukemia-free survival, OS : overall survival, RI : relapse incidence, NRM : non relapse mortality, CI : cumulative incidence , GVHD : graft-versus-host-disease