ARTICLE

Salvage therapy with high-dose cytarabine and mitoxantrone in combination with all-trans retinoic acid and gemtuzumab ozogamicin in acute myeloid leukemia refractory to first induction therapy

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ABSTRACT

Outcome of patients with primary refractory acute myeloid leukemia remains unsatisfactory. We conducted a prospective phase II clinical trial with gemtuzumab ozogamicin (3 mg/m^2 intravenously on day 1), all-*trans* retinoic acid (45 mg/m^2 orally on days 4-6 and 15 mg/m^2 orally on days 7-28), high-dose cytarabine (3 g/m^2/12 h intravenously on days 1-3) and mitoxantrone (12 mg/m^2 intravenously on days 2-3) in 93 patients aged 18-60 years refractory to one cycle of induction therapy. Primary end point of the study was response to therapy; secondary end points included evaluation of toxicities, in particular, rate of sinusoidal obstruction syndrome after allogeneic hematopoietic cell transplantation. Complete remission or complete remission with incomplete blood count recovery was achieved in 47 (51%) and partial remission in 10 (11%) patients resulting in an overall response rate of 61.5%; 33 (35.5%) patients had refractory disease and 3 patients (3%) died. Allogeneic hematopoietic cell transplantation was performed in 71 (76%) patients; 6 of the 71 (8.5%) patients developed moderate or severe sinusoidal obstruction syndrome after transplantation. Four-year overall survival rate was 32% (95% confidence interval 24%-43%). Patients responding to salvage therapy and undergoing allogeneic hematopoietic cell transplantation (n=51) had a 4-year survival rate of 49% (95% confidence interval 37%-64%). Patients with fms-like tyrosine kinase internal tandem duplication positive acute myeloid leukemia had a poor outcome despite transplantation. In conclusion, the described regimen is an effective and tolerable salvage therapy for patients who are primary refractory to one cycle of conventional intensive induction therapy. (*clinicaltrials.gov identifier: 00143975*)

Introduction

The prognosis of patients with acute myeloid leukemia (AML) refractory to first induction chemotherapy is poor. About 15%-20% of younger patients (<61 years) are primary refractory to one cycle of standard 7+3 induction chemotherapy.[1-3] Substantial long-term survival in this patient population has only been observed if allogeneic hematopoietic cell transplantation (HCT) was performed, resulting in overall survival (OS) rates of 10%-31% measured from date of HCT.[4-9] Best outcome after allogeneic HCT is achieved when transplantation is performed in complete remission (CR) or partial remission (PR) after salvage therapy.[6,8,9] Therefore, better response rates to salvage therapy are crucial to improve OS in these patients.

Different high-dose cytarabine-based salvage regimens, often used in combination with anthracyclins and epipodophyllotoxins, resulted in CR rates between 11% and 70%.[3] In order to increase CR rates, high- or intermediate-dose cytarabine has been combined with a wide spectrum of different drugs such as idarubicin and fludarabine (FLAG-Ida), clofarabine, gemtuzumab ozogamicin (GO), and all-*trans* retinoic acid (ATRA).[10-13] The German-Austrian AML Study Group (AMLSG) evaluated the conventional (HAM) and a sequential (S-HAM) HAM regimen in patients with refractory disease. No beneficial effect could be shown with the dose-intense S-HAM regimen.[14] In the subsequent trial, AML HD98A, ATRA was added to the HAM regimen (A-HAM) based on promising *in vitro*[15,16] and *in vivo* data.[17,18] The sequential administration of ATRA after HAM led to an overall response rate of 47% and was thus remarkably better than HAM alone.[9] In line with our data, Montillo *et al*. reported a CR rate of 70% induced by a salvage therapy combining ATRA with fludarabine, cytarabine, idarubicin, and granulocyte-colony stimulating factor (G-CSF).[10]

Several phase I-II clinical trials evaluating GO in relapsed/refractory AML showed response rates up to 33% when used as single agent, and 12%-68% in combination with chemotherapy.[13,19,20] Based on these promising results, we combined GO with our previously established A-HAM regimen (GO-A-HAM) in patients refractory to one cycle of 3+7-based induction therapy. The main objectives of the study were to assess GO-A-HAM with regard to response rate, toxicity [including sinusoidal obstruction syndrome (SOS)] after allogeneic HCT, and survival.

Table 1. Clinical and genetic characteristics at diagnosis and study entry.

Characteristics	At diagnosis	At study entry
Age, years		
Median (range)	48 (22-62)	
Sex, n. (%)		
Male	45 (48)	
Female	48 (52)	
Type of AML, n. (%)		
De novo	77 (83)	
s-AML	4 (4)	
t-AML	12 (13)	
Cytogenetics risk, n. (%)		
CBF-AML	3 (3.5)	
Intermediate	48 (58)	
Adverse*	32 (38.5)	
Missing	10	
Mutated-NPM1, n. (%)	12 (15)	
Missing	14	
FLT3-ITD, n. (%)	18 (22)	
Missing	10	
WBC, x 10^9/L		
Median (range)	16.0 (0.6-243.6)	1.41 (0.1-7.1)
Missing	0	3
Platelets, x10^9/L		
Median (range)	74 (5-585)	33.5 (2-223)
Missing	0	3
Hemoglobin, g/dL		
Median (range)	9.1 (5.0-13.3)	9.35 (6.80-12,5)
Missing	0	3
Bone marrow blasts, %		
Median (range)	70 (7-100)	60 (5.5-100)
Missing	5	4
Peripheral blood blasts, %		
Median (range)	47 (0-100)	4.5 (0-46)
Missing, n.	3	19
CD33 expression		
Cut off at 20%, n. (%)		
Positive	70 (86%)	
Missing, n.	12	

*s-AML: secondary AML after preceding MDS; t-AML: therapy-induced AML; CBF: core binding factor; NPM1: nucleophosmin; FLT3-ITD: FMS-like tyrosine kinase 3 gene internal tandem duplication; WBC: white blood count. *According to European LeukemiaNet recommendations.[1]*

Methods

Patients

Patients 18-60 years of age with AML defined by the 2001 World Health Organization Classification of Tumours[21] who did not achieve a CR, CR with incomplete blood count recovery (CRi) or partial remission (PR) after one cycle of standard chemotherapy, and who had adequate organ function, were eligible for entry into the trial. Patients with acute promyelocytic leukemia and patients with a concomitant uncontrolled infection were not eligible. Written informed consent was obtained from all patients at study entry according to the Declaration of Helsinki. The study was approved by the local Ethics Review Committee and registered at *clinicaltrials.gov identifier: 00143975*.

Study design

The trial was a single-arm multi-center phase II trial. All patients received one cycle of GO-A-HAM consisting of GO 3 mg/m² intravenously (IV max. 5 mg absolute) over two hours on day 1; cytarabine 3 g/m² every 12 hours IV on days 1-3; mitoxantrone 12 mg/m² IV days 2 and 3; oral all-*trans* retinoic acid 45 mg/m² on days 4-6 and 15 mg/m² on days 7-28. In all patients, allogeneic HCT from a matched related or matched unrelated or from a haploidentical family donor was intended irrespective of the remission status after GO-A-HAM.

Table 2. Overall treatment response.

Parameter	Patients (n=93)	
Complete remission	28	(30%)
Complete remission with incomplete blood count recovery	19	(20%)
Partial remission	10	(11%)
Overall response rate	57	(61%)
Refractory disease	33	(35%)
Early death	3	(3%)

Statistical analyses, efficacy and safety end points

The primary end point of the study was achievement of CR or CRi at a maximum of 30 days after start of therapy with GO-A-HAM defined by standard criteria.[22] Beyond CR/CRi, partial remission (PR) defined according to standard criteria[22] was documented and evaluated. A continuous safety assessment was performed during the study. Toxicities reported during therapy were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), v.3.0. The safety end points with corresponding maximally tolerated rates were: i) NCI-CTC grade 4+5 liver toxicity ≤ 10%; ii) rate of deaths within 30 days after start of GO-A-HAM 25% or under; and iii) rate of severe SOS after allogeneic HCT or under 20%. SOS was defined according to the Baltimore criteria[23] and graded as described by Bearman.[24] Management of SOS followed local standard operating procedures of the respective transplantation centers.

Univariable and multivariable logistic regression models were used to test the influence of covariates on response to induction therapy.

The Kaplan-Meier method was used to estimate the distribution of OS. Survival distributions were compared using the log rank test. To address the time dependence of the variable allogeneic HCT, a multivariable analysis based on an extended Cox regression model was used according to the method of Andersen and Gill.[25] Missing data were replaced by 50 imputations using multivariate imputations by chained equations applying predictive mean matching.[26] Backward selection applying a stopping rule based on *P*-values was used in multivariable regression models to exclude redundant or unnecessary variables.[26] For all analyses, $P<0.05$ was considered statistically significant. All eligible patients who started with GO-A-HAM were included in the analysis. Statistical analyses were performed with the statistical software environment R v.3.2.1 using the R package cmprsk, survival, rms and Hmisc.[27]

Results

Patients' characteristics

From July 2004 to June 2007, 95 patients from 23 institutions fulfilled the eligibility criteria and were enrolled in the study. Two patients withdrew their consent before initiation of treatment; thus, a total of 93 patients are reported. Prior treatments of the patients were as follows: 29 patients received standard induction therapy with idarubicin, cytarabine, and etoposide (ICE), 26 patients ICE in combination with ATRA (A-ICE), 17 patients with valproic acid (V-ICE), and 12 patients with both ATRA and valproic acid (VA-ICE), according to the initial randomization of the AMLSG 07-04 protocol (*clinicaltrials.gov identifier: 00151242*);[28] 9 patients were treated in the German AML Intergroup trial[29] and received standard induction therapy with daunorubicin and cytarabine (DA). Median age was 48 years (range 22-62 years); further demographics and baseline characteristics of the 93 patients are shown in Table 1. Eighteen of 83 (22%) patients had an fms-like tyrosine kinase internal tandem duplication (*FLT3*-ITD) mutation and 12 of 79 (15%) patients a nucleophosmin (*NPM1*) mutation at time of initial diagnosis. The surface marker CD33 was expressed in 87% of the patients with a 20% expression cut-off level.

Response rate and treatment outcome

Twenty-eight patients (30%) achieved CR, 19 patients (20%) CRi, and 10 patients PR (11%), resulting in an overall response rate of 61%; 33 patients (35%) were refractory and 3 patients (3%) died within 30 days (Table 2).

Multivariable analysis on the end point CR/CRi or overall response revealed no prognostic influence of the following variables assessed at diagnosis: age, sex, cytogenet-

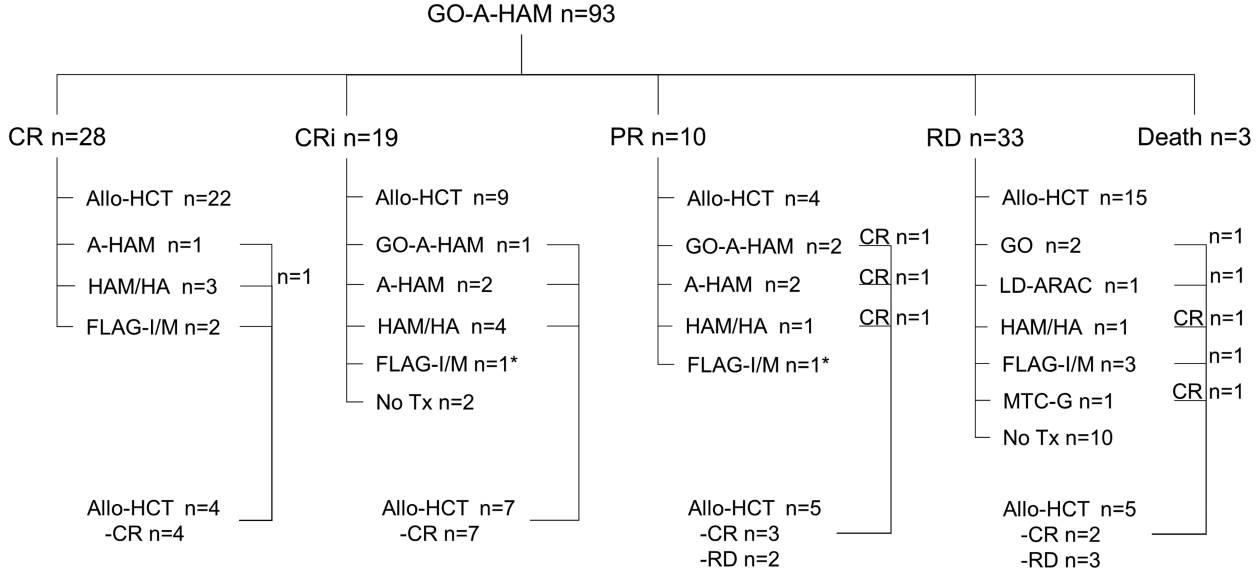

Figure 1. Flow chart on study conduct. Flow-chart showing subsequent treatment and outcome according to response to GO-A-HAM. A: all-*trans* retinoic acid; Allo-HCT: allogeneic hematopoietic cell transplantation; CR: complete remission; CRi: CR with incomplete hematologic recovery; FLAG-I/M: fludarabin, cytarabine, G-CSF+ idarubicin or mitoxantrone; GO: gemtuzumab ozogamicin; HA high-dose cytarabine; HAM: high-dose cytarabine and mitoxantrone; LD-ARAC: low-dose cytarabine; MTC-G: mitoxantrone, topotecan, cytarabine, imatinib; PR: partial remission; RD: refractory disease.

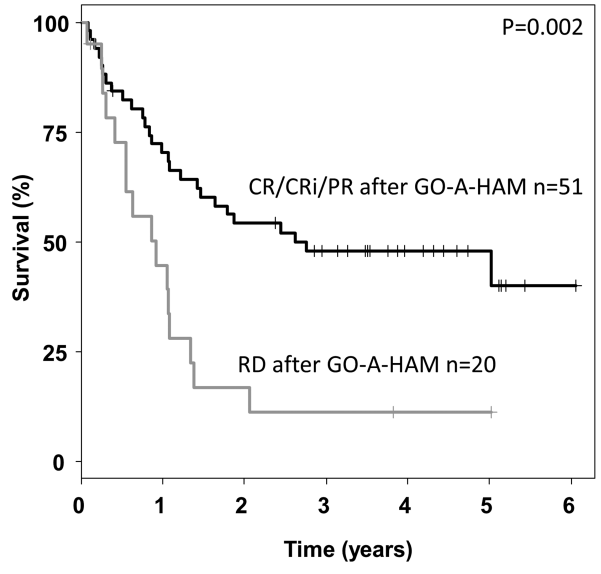

Figure 2. Survival after allogeneic hematopoietic cell transplantation according to response to GO-A-HAM salvage therapy.

ics (according to European LeukemiaNet criteria),[1] white cell count (WBC), bone marrow blast percentage, type of AML [*de novo versus* secondary AML evolving from myelodysplastic syndrome (AML) *versus* therapy-related AML (t-AML)], CD33 expression, mutated *NPM1*, *FLT3*-ITD and prior treatment with ATRA. Of note, patients with t-AML had a nearly equal CR/CRi rate of 50% compared to *de novo* AML with 53%, whereas none of the 4 patients with s-AML responded to GO-A-HAM.

Toxicity

Hematologic toxicity

Median times of WBC (>1x10^9/L), neutrophil (>0.5x10^9/L) and platelet (>20x10^9/L) recovery were 22, 25 and 21 days, respectively.

Non-hematologic toxicity

In 60 (65%) of the 93 patients, a total of 86 infections with a CTC grade 3 or over occurred. The most frequent infections were septicemia (n=43; 46%), pneumonia (n=20; 22%), and infections of the gastrointestinal tract (n=11; 12%). Other infection sites included skin and soft tissue (n=5; 5%), ear-nose-throat (n=3; 2%), urogenital tract (n=1; 1%), liver (n=1; 1%), and esophagus (n=1; 1%) (Table 3). Five patients died of severe infection, including 3 patients who died within 30 days after start of GO-A-HAM.

Other non-hematologic toxicities were seen in 30 patients, and 42 adverse events with a CTC grade 3 or more were reported (Table 4). The most common events were gastrointestinal toxicities (n=14) including diarrhea, nausea and mucositis, and neurological symptoms (n=10) with polyneuropathy, ataxia and hallucination. Cardiac events [tachyarrhythmia absoluta, left ventricular failure (n=2), pericardial effusion and pericarditis] occurred in 5 patients. A total of 4 episodes of hemorrhage CTC grade 3 were noted during treatment, two central nervous system bleedings, one vaginal bleeding, and one bleeding after central venous system installation. Four patients developed respiratory insufficiency. An additional 3 events of thrombosis were reported, two of them located in the internal jugular vein. One patient experienced renal failure. SOS was not observed during or after GO-A-HAM. Median duration of hospitalization was 27.5 days (range 8-96 days).

Table 3. Infectious complications.

Infection site	Grade 1/2	Grade ≥3
Septicemia		43 (46%)
Pulmonary	1 (1%)	20 (22%)
Gastrointestinal	2 (2%)	11 (12%)
Skin/soft tissue	1 (1%)	5 (5%)
ENT	2 (2%)	3 (3%)
Esophagus		1 (1%)
Liver		1 (1%)
Urogenital		1 (1%)
Other	1 (1%)	1 (1%)
Grading according CTC NCI version 3		

Grading according to the National Cancer Institute's Common Terminology Criteria for Adverse Effects v.3. ENT: ear/nose/throat.

Table 4. Non-hematologic adverse events (excluding infection).

Adverse event	Grade 1/2	Grade ≥3
Gastrointestinal		14 (15%)
Neurological	1 (1%)	10 (11%)
Cardiac		5 (5%)
Pulmonary		4 (4%)
Hemorrhage		4 (4%)
Thrombosis		3 (3%)
Renal	1 (1%)	1 (1%)
Liver		2 (2%)
Pain		2 (2%)
Endocrine	2 (2%)	1 (1%)
Skin	2 (2%)	
General condition	2 (2%)	

Grading according to the National Cancer Institute's Common Terminology Criteria for Adverse Effects v.3.

Subsequent treatment

Consolidation therapy with allogeneic HCT was performed in 71 of 93 patients (76%); 51 patients achieved CR, CRi or PR after GO-A-HAM, and 20 patients had persistent refractory disease. Reasons for not proceeding to an allogeneic HCT were death after GO-A-HAM (n=3), comorbidities and bad performance status (n=12), no compatible donor (n=3) and patients' wish (n=4). Of the 71 patients who received allogeneic HCT, 50 patients proceeded immediately to allogeneic HCT, 19 patients received one or two additional cycles of intensive chemotherapy [A-HAM, n=5; HAM/high-dose cytarabine, n=9; GO-A-HAM, n=3; high-dose cytarabine with mitoxantrone and topotecan (*clinicaltrials.gov identifier: 00744081*), n=1; fludarabine, cytarabine, G-CSF (FLAG),±idarubicin/mitoxantrone, n=1], one patient received GO as single agent, and one received low-dose cytarabine (Figure 1). Median time from start of therapy with GO-A-HAM to allogeneic HCT was 70 days; 16

patients were transplanted from matched related donors, 50 patients from matched unrelated donors, and 5 patients from haplo-identical related donors. Myeloablative conditioning regimens (n=34) included cyclophosphamide (Cy) and total body irradiation (TBI-Cy) or busulfan and Cy (Bu-Cy) (n=26), Bu-Cy with radioimmunotherapy (RIT) (n=6),[30] and fludarabine, melphalan and thiotepa (n=2). Dose-reduced conditioning regimens (n=37) included FLAMSA-based regimens (n=24),[31] fludarabine plus total body irradiation (n=6), fludarabine plus busulfan (n=2), fludarabine plus melphalan+/-BCNU (n=3), and fludarabine plus or threosulfan (n=2). OS after allogeneic HCT with myeloablative and dose-reduced conditioning was comparable (*P*=0.54).

Of 19 patients not proceeding to allogeneic HCT, 7 received additional cycles of intensive therapy (HAM/high-dose cytarabine n=2, single agent GO, n=1; FLAG±idarubicin/mitoxantrone, n=4) followed by autologous HCT in 2 patients. Twelve patients received no further intensive treatment (Figure 1).

Sinusoidal obstruction syndrome after allogeneic HCT and safety analysis according to predefined safety end points

Nine patients developed SOS after allogeneic HCT; in 3 patients SOS was classified as mild, in 5 patients as moderate, and one patient died of severe SOS, leading to a rate of moderate/severe SOS of 8.5% (95%CI: 3.9%-17.2%). In 7 of 34 patients, SOS occurred after myeloablative conditioning, including the patient who died from SOS, whereas only 2 of 37 patients developed SOS after dose-reduced conditioning (*P*=0.08). Grade 4/5 liver toxicity was not observed. The rate of early and hypoplastic death within 30 days after start of GO-A-HAM was 3%. All rates were below the maximally tolerated death-rate predefined in the protocol.

Survival analysis

Median follow up for survival was 48.8 months. In total, 62 of the 93 patients died; median OS was 16.0 months and the 4-year OS rate 32% (95%CI: 24%-43%) for the whole cohort. OS at four years after start of treatment was poor (7%, 95%CI: 1%-42%) in patients not proceeding to allogeneic HCT (n=22). In patients proceeding to allogeneic HCT (n=71), 4-year OS after transplant was 39% (95%CI: 29%-52%), with a significantly better OS (*P*=0.0006) (Figure 2) since the timepoint of allogeneic HCT in patients (n=51) responding to GO-A-HAM (49%, 95%CI: 37%-64%) compared to those (n=20) not responding (11%, 95%CI: 3%-41%); there was no difference in outcome in responding patients according to type of response (i.e. CR, CRi, PR; *P*=0.48). An Andersen Gill regression model (Table 5) on OS after GO-A-HAM with allogeneic HCT as a time-dependent co-variable after limited backward selection revealed allogeneic HCT (*P*=0.04) and response to GO-A-HAM (*P*<0.0001) as prognostic favorable variables, whereas adverse cytogenetics according to European LeukemiaNet1 criteria (*P*=0.09), older age (*P*=0.04), s-AML/t-AML (*P*=0.02) and *FLT3*-ITD (*P*=0.04) were unfavorable parameters. All 18 patients with *FLT3*-ITD positive AML proceeded to allogeneic HCT (n=13 responded to GO-A-HAM), but outcome was poor despite allogeneic HCT (Figure 3).

Table 5. Anderson Gill regression model on overall survival including allogeneic HCT as time-dependent co-variable.

	HR	*P*
Allogeneic HSCT	0.47	0.04
Response (CR, CRi, PR) to GO-A-HAM	0.24	<0.0001
Age in years, 10-year difference	1.35	0.04
s/t-AML	2.16	0.02
Adverse cytogenetics[1]	1.64	0.09
FLT3-ITD	2.13	0.04

Parameters withdrawn by limited backward selection; WBC, CD33 expression, sex, NPM1 mutational status, prior treatment with ATRA. Results of univariable Cox-regression analyses: response to GO-A-HAM (HR 0.27; P<0.0001). Age in years (HR for a 10-year difference 1.46; P=0.004), s/t-AML (HR 3.22; P=0.0001), adverse cytogenetics[1] (HR 2.05; P=0.01), FLT3-ITD (HR 1.66; P=0.11); log10(WBC) (HR 1.12; P=0.53), CD33 expression with 20% cut off (HR 0.93; P=0.86), male sex (HR 1.12; P=0.65), mutated NPM1 (HR 0.98; P=0.96). HCT: hematopoietic cell transplantation; s/t-AML: secondary AML after preceding MDS/therapy-induced AML; FLT3-ITD: FMS-like tyrosine kinase 3 gene internal tandem duplication; WBC: white blood count; NPM1: nucleophosmin.

Discussion

Here we report on the prospective phase II study evaluating the GO-A-HAM regimen consisting of gemtuzumab ozogamicin in combination with all-*trans* retinoic acid, high-dose cytarabine and mitoxantrone in patients with primary refractory disease. Primary refractory disease in this study was defined as AML not responding to one cycle of standard 3+7-based induction therapy with either CR, CRi or PR. Half of the patients achieved CR or CRi, and another 11% of patients achieved PR, leading to an overall response rate of 61% that compares favorably to those in previous AMLSG protocols which used the HAM and S-HAM[14] as well as A-HAM regimens[9] in this patient population.

Chevallier *et al.* reported on a similar salvage regimen combining intermediate-dose cytarabine with mitoxantrone and GO at a dosage of 9 mg/m^2 given on day 4 in refractory or relapsed AML patients.[13] Although a direct

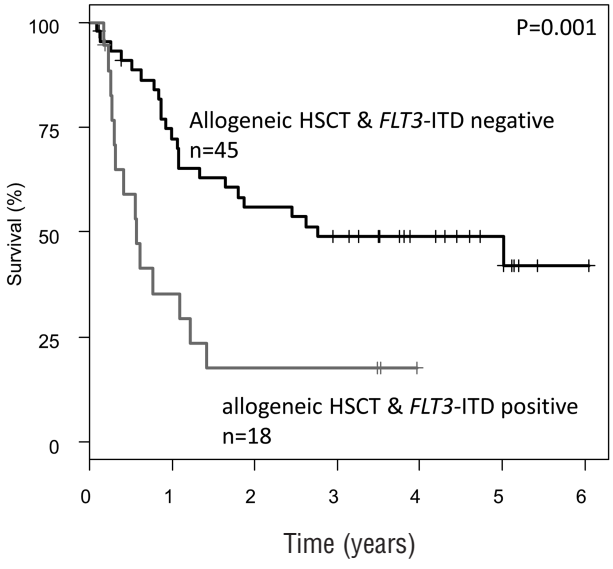

Figure 3. Kaplan-Meier plot illustrating prognostic impact of *FLT3*-ITD status in patients receiving an allogeneic hematopoietic cell transplantation measured from the date of transplantation.

comparison is difficult, the authors reported a CR rate of 39% in the refractory patient cohort. Whether the somewhat superior CR/CRi rate in our trial was due to the addition of ATRA remains elusive. Of note, in a large randomized trial in refractory/relapsed AML conducted by the Medical Research Council, no significant impact of ATRA as adjunct to intensive chemotherapy could be shown.[32] However, ATRA in this study was initiated at day 1 of chemotherapy raising the important issue of which is the best schedule with significant beneficial effects of ATRA when given after chemotherapy,[33] as in the GO-A-HAM regimen. Several clinical trials[20,34,35] and a meta-analysis[36] showed that GO given as adjunct to intensive induction chemotherapy improved several survival end points, in particular in patients with favorable or intermediate cytogenetic risk AML. Of note, GO was only effective if given early in the treatment course, i.e. in first induction therapy; however, there was no impact on the response rate.[36] Interestingly, the addition of GO to induction therapy was particularly effective in AML with *FLT3*-ITD based on a subset analysis.[34] However, this beneficial effect was based on a very small sample size and has not been confirmed by others.[35]

In our study, we were not able to identify prognostic factors for the response to GO-A-HAM. Compared to our historical controls,[9,14] GO had a major impact in improving CR rates in primary refractory patients mainly with adverse or intermediate cytogenetic risk profile. In fact, in our multivariable analyses on OS, adverse cytogenetics represented the only trend associated with an inferior outcome, with a much weaker impact compared to type of AML, age, and presence of *FLT3*-ITD (Table 5). Thus, our results do not support a beneficial effect of GO in AML with *FLT3*-ITD, despite the fact that all patients in our study of this subgroup proceeded to allogeneic HCT (Figure 3). To improve outcome of patients with *FLT3*-ITD positive AML, the incorporation of FLT3 inhibitors before and after transplantation is currently being evaluated in clinical trials (*clinicaltrials.gov identifers: 01477606, 01468467*, and *02298166*, and *EudraCT 2010-018539-16*).

The majority (76%) of enrolled patients could proceed to allogeneic HCT. Four-year OS since start of treatment of patients responding to GO-A-HAM and receiving allogeneic HCT was 49% compared to only 11% in patients who were refractory to salvage therapy. These results again underline the strong impact of the disease status at the time of transplantation on long-term survival, as has been previously reported.[5-7,9] Thus, the two major prerequisites for long-term survival in primary refractory patients are chemo-sensitivity to salvage therapy followed by allogeneic HCT.

An important point to consider when GO is added to intensive chemotherapy is the dosage, especially if allogeneic HCT is planned. In most regimens conducted in Europe, doses lower than 9 mg/m^2 (the dose originally approved by the US Food and Drug Administration in 2000 for single agent therapy) were applied. In our trial, a dosage of 3 mg/m^2 had only a modest impact on toxicity, especially with regard to the development of SOS directly after salvage therapy as well as after transplantation, with a rate of moderate/severe SOS after transplantation of 8.5%, which is expected in this patient population.[30,31,37,38] Thus, in contrast to previous data showing an enormously increased incidence of SOS (64%) by pre-treatment with GO (6 mg/m^2 or 9 mg/m^2) in a 3.5-month period prior to transplant,[39] we were able to show that salvage therapy including GO in a dosage of 3 mg/m^2 is safe and can be followed by allogeneic HCT without increasing the rate of SOS. Whether an increment of the GO dosage by using fractionated administration,[40,41] comparable to successful attempts in first-line therapy,[35] is safe in terms of SOS and even more effective compared to our GO-A-HAM regimens remains elusive.

In summary, the addition of GO in a dosage of 3 mg/m^2 and of ATRA to intensive chemotherapy in patients with AML refractory to one cycle of induction therapy resulted in a high response rate and a high proportion of patients proceeding to allogeneic HCT with very limited additional toxicity. However, primary refractory AML with *FLT3*-ITD still had a very poor outcome despite allogeneic HCT.

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