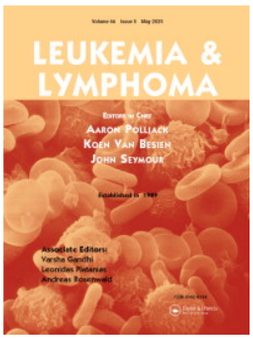

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Final analysis of the GMALL-PH-01 trial: phase II study of standard chemotherapy in combination with dasatinib in first line treatment of Philadelphia chromosome positive acute lymphoblastic leukemia

Fabian Lang[a], Andreas Voss[b], Guido Kobbe[c], Christian Junghanss[d], Joachim Beck[e], Andreas Viardot[f], Knut Wendelin[g], Jens Panse[h], Lisa Heberling[i], Vladan Vucinic[j], Boris Böll[k], Max Topp[l], Dieter Hoelzer[a], Hubert Serve[a], Nicola Goekbuget[a], Oliver G. Ottmann[m] and Heike Pfeifer[a]

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ABSTRACT

Imatinib (IMA) plus chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is established treatment for Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). We investigated the use of dasatinib (DASA) combined with intensive chemotherapy in ALL (18–55 years) first-line in a prospective, multicenter phase II trial by the GMALL study group. 140 mg DASA QD was used with a pediatric-based induction and consolidation chemotherapy according to GMALL 07/2003 protocol with recommended consecutive HCT. Nineteen of 20 planned patients were enrolled in 12 centers. The hematologic CR rate after induction was 79% with an overall MRD negativity rate of 62.5%. Six patients died during induction and two discontinued therapy. This regimen achieved deep molecular responses but was associated with a higher than expected early mortality (21%) and was stopped prematurely due to toxicities. The GMALL therefore adopted a combination of low intensity chemotherapy plus IMA as its current induction regimen.

Abbreviations: AE: Adverse event; ALL: Acute lymphoblastic leukemia; ALT: Alanin-Aminotransferase, ALAT, GPT; ANC: Absolute neutrophil count; AST: Aspartat-Aminotransferase, ASAT, GOT; BCR-ABL: BCR-ABL oncoprotein product of bcr-abl fusion gene; BfArM: Bundesamt für Arzneimittel und Medizinprodukte; c-ALL: All subtype, Common ALL; CNS: Central nervous system; CR: Complete remission; CCR: continous complete remission; CP: Cyclophosphamide; CRF: Case report form; CTCAE: Common terminology criteria for adverse events; DNR: Daunorubicine; DSUR: Development and safety update report (Annual safety report); EC: Ethics Committee; ECOG -: Eastern Cooperative Oncology Group; EOS: End of study; FPI: First patient in; GGT: Gamma-Glutamyl-Transferase; GMALL: German multicenter study group for adult ALL; Gy: Gray, radiation dose; HCT: Hematopoetic cell transplantation; ISF: Investigator site file; LPO: Last patient out; m-BCR-ABL: Minor BCR-ABL; M-BCR-ABL: Major BCR-ABL; MRD: Minimal residual disease; NOS: Not Other Specified; PI: Principal Investigator; Ph+: Philadelphia chromosome positive; PR: Partial Remission; QD: Quaque die, one per day; SAE: Serious adverse Event; SmPC: Summary of product characteristics; SUSAR: Suspected unexpected serious adverse reaction; TBI: Total body irradiation; TMF-: Trial master file; TRM: Treatment-related mortality; VP16: Etoposide, etoposide phosphate; WBC: White blood count

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Introduction

ALL has an overall incidence of 1/100.000 with peaks in childhood and in older patients. Ph + ALL is present in roughly 20–50% of all adult ALL patients depending on age. The outcome in younger patients (< 55 years) has improved considerably over the past decade [1]. With the introduction of tyrosine kinase inhibitors (TKI) in combination with chemotherapy (chemo), CR rates after induction were above 90% and a higher proportion of patients became eligible for allogeneic hematopoietic cell transplantation (HCT). Overall Survival (OS) probability of approximately 60% at 5 years has been achieved in recent trials for younger, and of 30–40% for older patients, respectively [2,3]. The standard regimen in newly diagnosed adult Ph + ALL within the GMALL study group was IMA in combination with chemo followed by HCT. The 2nd generation TKI DASA in combination with intensive chemotherapy (hyper CVAD), has proven feasibility and efficacy in patients with relapsed Ph + ALL or CML lymphatic blast phase (CML-LB) [4]. DASA has also been examined in combination with intensive chemotherapy as front-line therapy of younger adults with Ph + ALL [5], and in combination with lower dose chemotherapy in elderly Ph + ALL patients [6]. In pediatric patients, the combination of DASA with intensive chemotherapy showed reasonable efficacy and was well tolerated resulting in improved outcome [7]. In this framework, this study combined standard chemotherapy in adult ALL according to the GMALL 07/2003 protocol with DASA. The primary objective was to evaluate feasibility of this combined approach in adult ALL and enhance the rate of early molecular remissions. This might result in an improved overall remission duration and survival in combination with HCT.

Materials and methods

Study design

GMALL-PH-01 was an open label phase II pilot study of the German Multicenter Study Group for Adult ALL (GMALL) designed to include 20 patients at multiple GMALL sites. Patients who were enrolled but do not receive the first dose of DASA were replaceable. The trial was registered under the clinicaltrials.gov identifier NCT01724879. Target population was patients aged 18–55 years with newly diagnosed and previously untreated Ph + ALL. The spectrum of BCR::ABL1 mutations at baseline, time of relapse, end of treatment was planned to be assessed for all treated subjects. The study protocol was reviewed and approved by local authorities and written informed consent was obtained from all patients participating in this study. The study was designed and conducted in accordance to the declaration of Helsinki. End of study (EOS) was defined as patients receiving allo HCT or in case allo HCT was delayed for logistic or medical reasons, DASA administration was continued within the study until a maximum of 6 months after start of induction, or until additional consolidation chemotherapy was delivered. In case of allo HCT was not possible DASA treatment was conducted till day 120.

Statistical analysis

The trial was designed as an intention to treat analysis. The probability of relapse-free and overall survival was estimated by the nonparametric Kaplan-Meier method. The medians are presented with their 95% confidence intervals. Statistical analysis used the SAS 8.2 Software (SAS, Inc., Cary, NC). Twenty eligible subjects with newly diagnosed Philadelphia positive ALL were planned to be included in the study for assessment of feasibility. A death rate of greater than 20% during induction therapy and a discontinuation rate of greater than 35% by or before end of study treatment due to death or treatment-related toxicity would be considered to constitute nonfeasibility. If these thresholds were already exceeded before 20 patients were enrolled, the study would be stopped.

Objectives and endpoints

Primary objective was to evaluate the feasibility of a combination of DASA with standard chemotherapy in adult Ph + ALL patients. Secondary objectives included determination of the hematologic response rate, assessment of the molecular CR rate during combined DASA and chemotherapy treatment, assessment of the frequency and type of BCR::ABL1 tyrosine kinase domain mutations, rate of death during induction and death in complete remission. Primary endpoint was survival and rate of treatment-related discontinuation of study treatment during induction and consolidation. Secondary endpoints were defined as molecular CR rate and hematologic CR rate at end of induction II, BCR::ABL1 mutations occurring during treatment and Grade III and IV toxicity according to CTC V3.0.

Treatment

DASA was administered at a dose of 140 mg QD starting on day 1 of induction therapy (day 6 including

prephase) and continued throughout both induction cycles and consolidation I until allo HCT, which was scheduled after consolidation I approximately around day 120. In patients in whom allo HCT was not performed, DASA therapy stopped at day 120. Further treatment thereafter was investigators choice according to GMALL treatment recommendations. In case allo HCT was delayed DASA was administered within the study until a maximum of 6 months after start of induction. Prephase, induction cycles I and II and consolidation cycles as well as CNS prophylaxis were administered according to the GMALL protocol 07/2003. Prephase consisted of Dexamethasone 10 mg/m^2 p.o. on days 1–5, cyclophophamide 200 mg/m^2 i.v. on days 3–5 and Methotrexate 15 mg abs i.th. on day 1. Induction I consisted of dexamethasone 10 mg/m^2 p.o. on days 6–7 and 13–16, Vincristine 2 mg i.v. on days 6, 13, and 20 and PEG-Asparaginase 2000 U/m^2 i.v. on day 20. Induction II consisted of Cyclophosphamide 1000 mg/m^2 i.v. on days 26 and 46, Cytarabine 75 mg/m^2 i.v. days 28–31, 25–38, and 42–45, 6-MP 60 mg/m^2 p.o. on days 33–53 and Methotrexate 15 mg abs i.th. on days 28, 35 and 42. Prophylactic cranial irradiation (24 Gy) was also performed during induction phase II in patients achieving a CR after induction I. Consolidation I consisted of Dexamethasone 10 mg/m^2 p.o. on days 1–5, Vindesine 3 mg/m^2 i.v. on day 1, HD-methotrexate 1.5 g/m^2 i.v. on day 1, VP-16 250 mg/m^2 on days 4 and 5, HD-Cytarabine 2 × 2 g/m^2 i.v. on day 5, methotrexate (15 mg i.th), cytarabin (40 mg i.th.), and dexamethasone (4 mg i.th.) all on day 12. All chemotherapy cycles were accompanied by fixed regular administration of G-CSF starting at day 6 or 7 or continuously in case of initial neutropenia.

Patient assessment including molecular analyses

All accompanying investigations were conducted according to standard of care and included bone marrow aspiration with cytology, immunophenotyping by flow cytometry, cytogenetic and minimal residual disease (MRD) baseline analysis during initial patient workup. Bone marrow aspiration including quantitative BCR::ABL1 analysis was performed on days 11, 26, 46, 71 and at end of study (EOS). Peripheral blood analysis for BCR::ABL1 transcript quantification (% BCR::ABL1/ABL1) was also performed at these timepoints. Survival and remission status were assessed during follow up. At pretreatment and at each time of BCR::ABL1 quantification, blood and marrow samples were screened for BCR::ABL1 mutations by direct sequencing of BCR::ABL1. Analyses were performed according to [8,9]. BCR::ABL1 MRD was assessed according to definitions given in Table 6.

Results

Treatment course and patient characteristics

All nineteen patients who were included between Nov 2011 and Apr 2013 in 12 GMALL centers were evaluable with a median follow up of 579 days (1.59 years). The median age at study inclusion was 45 (range 31–53) years. Eight patients were older than 45 years. Ten of 19 patients showed a major BCR::ABL1 transcript (M-BCR::ABL1). None of the patients had CNS involvement. All other entry criteria are summarized in Table 1.

After induction I and II the complete remission rate was 79% (15 patients). No case of induction failure was observed and four patients (21%) died during induction (due to sepsis in neutropenia or hemorrhage). Therefore, all remaining patients achieved hematologic CR during induction and results are summarized in Table 2. For all 19 patients, BM results were available during or after induction, herein for 14 patients at day 26 and for 15 patients at day 46.

In the further course, 3 patients discontinued study treatment prematurely: One patient showed in induction a recurrent pleural effusion and discontinued and one patient discontinued study therapy due to liver-toxicity (both in CR). The remaining 13 patients showed a continuous complete remission on day 71 and received consolidation I. Neither a relapse nor a case of death

Table 1. Entry criteria.

		N = 19	%
Age	Median (range)	45 (31–53) years	
	18–24 years	0	0
	25–45 years	11	58
	46–55 years	8	42
Gender	Male	12	63
Immunophenotype	pre B-ALL	2	11
	c-ALL	17	89
BCR::ABL1 transcript	m-BCR	9	47
	M-BCR	10	53
ECOG	0	7	37
	1	10	53
	2	2	11
WBC (/µL)	Median (range)	26 600 (922 – 244,000)	
	> 30,000/ul	9	47
Granulocytes (/µL)	Median (range)	1304 (150 – 91,850)	
	< 500 /ul	6	32
Platelets (/µL)	Median (range)	41 000 (9000–958,000)	
	< 25,000 /ul	11	58
Blasts	Bone marrow	90% (40–100%)	
	Peripheral blood	60% (0–92%)	
Symptoms and organ involvement at screening	CNS involvement	0	0
	Enlarged lymph nodes	7	37
	Liver Enlargement	5	26
	Spleen Enlargement	8	42
	Infections	4	21

Table shows all entry criteria of the patients treated in the GMALL-PH01 trial.

Table 2. Remission results in induction.

	Day 26		Day 46		Overall results after induction	
	N	%	*N*	%	*N*	%
Evaluable	14		18		19	
CR	12	86	14	78	15	79
Early death	0	0	4	22	4	21
PR/Failure	2	14	0	0	0	0

Showing favorable remission results in and after Induction but with a significant early death rate.

was observed in any patient during the further treatment course. During consolidation I one patient discontinued study prematurely in CR due to renal toxicity, which was attributed to the underlying chemotherapy with high-dose methotrexate (MTX). The end of study (EOS) was scheduled on day 120. The median time to EOS was 118 (104–136) days and all 12 remaining patients were in continuous complete remission at EOS.

Dasatinib therapy and toxicities

DASA therapy started on day 6 ($N=8$), day 7 ($N=7$) or day 8 ($N=4$) of the underlying chemotherapy regimen. DASA was interrupted during induction I in only two patients. In one patient, an interruption was due to a pleural effusion This patient restarted DASA in induction II with a reduced dose of 100 mg QD and discontinued the study after the reoccurring pleural effusion as already described. In induction II, DASA interruption associated with toxicities grade 3 or 4 was necessary in 5 cases: Liver enzymes/bilirubin ($N=3$), cytopenia ($N=3$), coagulation ($N=2$) and/or nausea ($N=1$). Between day 46 and 71, DASA treatment interruptions were observed in 6 patients. Reasons were cytopenia ($N=4$) or liver toxicities ($N=2$). In one case of liver toxicity, the dose was modified to 100 mg QD, subsequently until EOS. In consolidation I, interruptions occurred in 3 patients. In one patient associated with stomatitis and in another associated with cytopenia. The reason for interruption was unclear in one patient.

The median interval between consolidation I and EOS was 32 days. During this time one case of pericardial effusion and another of CNS hemorrhage was observed. In both cases, regular EOS was performed. Three additional patients stopped DASA for at least one day during this period. Two of them showed cytopenia and mucositis, one patient developed also an edema.

In another patient, elevated liver enzymes (AST, ALT) were observed and after interruption of DASA application for several days a reduced does of 100 mg was administered until regular EOS.

Since the majority of low-grade toxicities was expected from the underlying chemotherapy and is well known and documented in historic cohorts, the documentation of adverse events was restricted to CTC grade 3–5. The only exception was pleural effusion as typical and known complication of DASA therapy which had to be documented at any degree.

The most common AE was cytopenia, as expected from the underlying chemotherapy. Toxicity was documented according to the CTC-AE V 3.0. The incidence of AEs is available in Table 3. Regarding the patients showing Grade 3/4 neutropenias the median (range) in days was 18 (7–20) in induction I, 14 (3–16) in induction II, 11.5 (4–24) on day 46 till day 71 and 4 (4–10) in consolidation I. In this respect 16 (84%) patients received G-CSF in induction I, 18 (95%) in induction II and 11 (85%) in consolidation I.

A total of 13 SAEs in 13 patients have been reported. Nine of these events have been classified as Serious Adverse Reaction (SAR) (Table 4).

Two cases of fatal sepsis were reported as SAE. One fatal subdural bleeding occurred in association with thrombocytopenia grade 3 in induction phase II. A second subdural and cerebral bleeding was observed after consolidation I and resolved. Both cases of CNS hemorrhage have been assessed as possibly related to DASA. CNS bleeding, also with fatal outcome is documented in the SmPC for DASA and is also known as a potential adverse event associated with the use of tyrosine kinase inhibitors. One fatal lung bleeding occurred in association with thrombocytopenia grade 4 during induction phase II. In one patient a seizure occurred and subsequently a temporary behavioral change was reported as SAE. The case was classified as neurological event. Magnetic resonance imaging was performed and revealed lesions; potential leukemic infiltration and/or an inflammatory process was suspected. The event was assessed as unlikely related to DASA. The MRI later on also revealed small subdural hygromas and a partial cortical postcentral vein thrombosis. All other non-fatal SAEs are described in Table 4. All fatal SAEs are summarized in Table 5.

Study treatment had to be discontinued prematurely due to toxicities (renal, liver, pleural effusion) in three patients in induction II ($N=2$) or after consolidation ($N=1$). The cases of renal toxicity and liver toxicity leading to premature stop of study treatment have also been reported as SAEs (see Table 5).

Outcome

Overall survival in 19 patients was 68% at one year (Figure 1) with similar disease-free survival. Survival of patients in CR ($n=15$) and after allo HCT ($n=14$) was 87 and 86% at 2 years, respectively (Figures 2 and 3).

Table 3. Adverse events grade 3–4, SAEs of any grade or pleural effusion of any grade.

Category	Adverse event	Frequency (Grade 3–4; absolute (%)) Induction I $N=19$	Frequency (Grade 3–4; absolute (%)) Induction II $N=19$	Frequency (Grade 3–4; absolute (%)) Day 46–71 $N=14$	Frequency (Grade 3–4; absolute (%)) Consolidation I ($N=13$)	Frequency (Grade 3–4; absolute (%)) Consolidation I – EOS) ($N=12$)
ALLERGY/IMMUNOLOGY	Allergy-Other (FFP associated)	1 (5%)	0	0		
BLOOD/BONE MARROW	Hemoglobin	6 (32%)	8 (42%)	7 (50%)	6 (46%)	5 (45%)
	Leukocytes	7 (37%)	6 (32%)	3 (21%)	2 (15%)	3 (27%)
	Neutrophils	4 (21%)	5 (26%)	4 (29%)	4 (31%)	4 (36%)
	Platelets	10 (53%)	10 (53%)	7 (50%)	5 (38%)	6 (55%)
CARDIAC GENERAL	Hypertension	1 (5%)	0			
	Pericardial effusion (grade 1)					1 (9%)
DERMATOLOGY/SKIN	Rash, Dermatitis - Radiation	0	1 (5%)	1 (7%)		
COAGLUATION	Fibrinogen	2 (11%)	12 (11%)			
	Other ATIII deficiency	0	3 (16%)			
CONSTITUTIONAL	Fatique	0	0	1 (7%)		
GASTROINTESTINAL	Anorexia / Nausea	1 (5%)	3 (16%)	3 (21%)		
	Diarrhea	2 (11%)	0			1 (9%)
	Dysphagia	0	1 (5%)			
	Mucositis/stomatitis				4 (31%)	5 (45%)
	Vomiting					2 (18%)
HEMORRHAGE/BLEEDING	Hemorrhage, GU – Vagina	1 (5%)				1 (9%)
	Hemorrhage, Central Nervous System	0	1 (5%) Grade 5			
	Hemorrhage, pulmonary	0	1 (5%) Grade 5			
	Hemorrhage - Rectal					1 (9%)
INFECTION	Febrile Neutropenia	1 (5%)	2 (11%)	1 (7%)	1 (8%)	
	Sepsis associated with multi-organ failure	0	2 (11%) Grade 5			
	Infection - Abdomen	0	1 (5%)			
	Infection -auditory/ear - middle ear			1 (7%)		
	Infection - General - NOS			1 (7%)		
	Infection - Anal/perianal -			1 (7%)		
	Infection - Pulmonary/ upper respiratory - Lung				1 (8%)	1 (9%)
METABOLIC/LABORATORY	ALT	1 (5%)	3 (16%)	2 (14%)	1 (8%)	2 (18%)
	AST	0	1 (5%)	1 (7%)	1 (8%)	2 (18%)
	Bilirubin	0	4 (21%)	2 (14%)		
	Creatinine				1 (8%)	
	GGT	1 (5%)	3 (16%)	3 (21%)	1 (8%)	1 (9%)
	Metabolic/Lab- Other (FSP D-Dimer)	1 (5%)	0			
NEUROLOGY	Depression	0	1 (5%)			
	Personality/behavioral (grade 2, but SAE reported)	1 (5%)				
	Neuropathy: sensory	1 (5%)				
	Seizure (grade 2, but SAE reported)	1 (5%)				
OCULAR/VISUAL	Eylid dysfunction			1 (7%)		
PAIN	Pain - Neurology - Head/ headache	1 (5%)	2 (11%)	2 (14%)		
	Pain - Pulmonary/Upper respiratory - throat/ pharynx/larynx	1 (5%)				
RENAL/GENITOURINARY	Renal failure				2 (16%)	1 (9%)
PULMONARY/UPPER RESPIRATORY	Pleural effusion (grade 2)	2 (11%)	2(11%)	1 (7%)		
	Pulmonary/Upper respiratory-Other (Pulmonary edema) (grade 2)	1 (5%)				
VASCULAR	Thrombosis/thrombus/ embolism			1 (7%)	1 (8%)	

Table shows all adverse events of higher Grade (3–4), all SAEs and as AEs of special interest any grade of pleural effusion. Grading has been performed according to CTC-AE V3.0.

Table 4. Cumulative summary tabulations of serious adverse events and grade 5 SAEs.

System Organ Class	SAEs N	Grade 5 N
Gastrointestinal		
Vomiting (associated with Hemorrhage, gastrointestinal)	1	
Hemorrhage/bleeding		
Hemorrhage, Central Nervous System	2	1
Hemorrhage pulmonar	1	1
Infection		
Infection with grade 3 or 4 Neutropenia	2	2
Metabolic/laboratory		
One or more of the following liver associated: ALT,GPT/AST,GOT/ Bilirubin	5	
Creatinine	1	
Neurology		
Seizure (associated with Personality/ behavioral)	1	

Table shows all serious adverse events and fatal SAEs which have been graded according to CTC-AE V3.0.

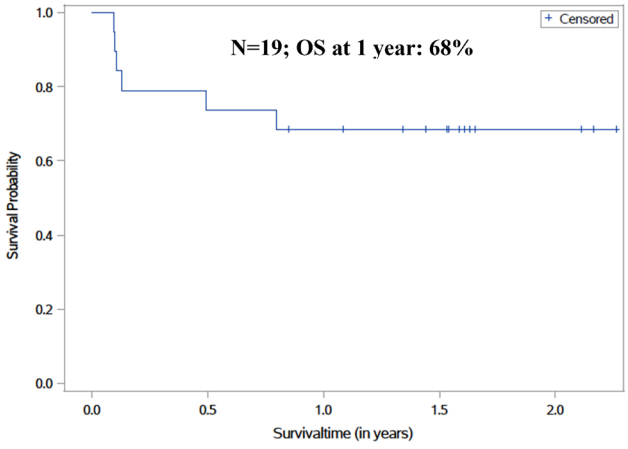

Figure 1. Overall survival. Figure shows the overall survival at one year of all 19 patients treated within the GMALL-PH01 trial.

Molecular response

On day 11, MRD analysis was performed in 13 patients. All patients remained MRD positive. On days 26 and 46, 33 and 40% of evaluable patients were MRD negative (Mol CR and Mol NE4), respectively. On day 71, 37.5% of evaluable patients were MRD negative (Mol CR und Mol NE4) and at the end of study finally 62.5% of the evaluable patients achieved MRD negativity (see Table 6).

Mutation analyses by sequencing the BCR::ABL1 transcript were performed at diagnosis and in patients with molecular failure (Day 26: $N=7$; Day 46: $N=2$; Day 120: $N=2$). All sequencings revealed a BCR::ABL1 wild type in the binding area of DASA.

Table 5. Summary and characteristics of grade 5 fatal SAEs and factors leading to end of trial.

Grade 5 SAE / Reason for EOS	Gender	Age	Timepoint	Contributing factors	Fatal
Hemorrhage, CNS	Male	53	Induction phase II	Thombocytopenia due to chemotherapy	Yes
Hemorrhage pulmonar	Male	51	Induction phase II	Thombocytopenia due to chemotherapy	Yes
Sepsis	Male	50	Induction phase II	Neutropenia due to chemotherapy	Yes
Sepsis	Female	49	Induction phase II	Neutropenia due to chemotherapy	Yes
Pleural effusion	Female	32	Induction phase II	n.a.	No
Liver enzyme elevation	Male	43	Induction phase II	Chemotherapy	No
Creatinin increase	Female	38	Consolidation I	Delayed high dose MTX Rescue	No

Table shows a summary and further characterization of all fatal SAEs and all factors which lead to end of trial.

Table 6. Results of MRD analysis in BM.

	Day 11 $N=19$	Day 26 $N=19$	Day 46 $N=14$	Day 71 $N=13$	Day 120 $N=12$
Evaluable	13	12	10	8	8
Mol CR: BCR::ABL1 negativity with a sensitivity of ABL1 > 10,000 copies		2		3	1
Mol Fail: BCR::ABL1 positivity with BCR::ABL1 > 10 copies and >1E−4	11	6	3	1	3
Mol NE1: MRD positive with BCR::ABL1/ ABL1 < 1E-04, not quantifiable (BCR-ABL < 10 copies, ABL > 10,000 copies)				1	
MolNE2: MRD positive below BCR::ABL1/ ABL1 < 1E−04, quantifiable (BCR-ABL > 10 copies, ABL > 10,000 copies)			1		
MolNE3: MRD positive not quantifiable, BCR::ABL1 < 10 copies, BCR::ABL1/ ABL1 > 1E-04	1	2	2	3	
MolNE4: MRD negative, not sufficient sensitivity (ABL1 < 10,000 copies)	1	2	4		4
MolNE6: No MRD material taken	6	7	4	5	4

Table shows the results of MRD assessment in the bone marrow including the classification having been used regarding number of BCR::ABL1 copies in relation to number of control gene (ABL).

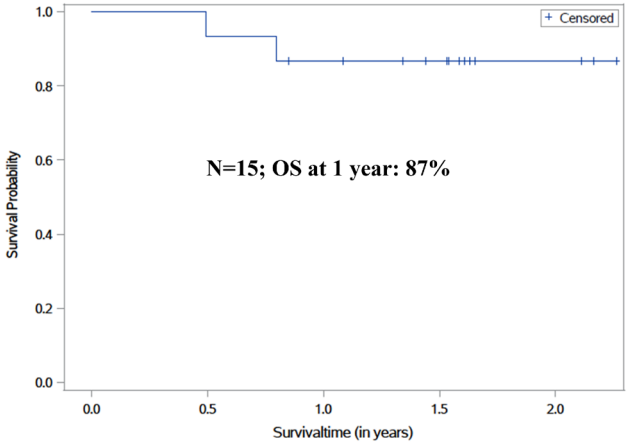

Figure 2. Survival of CR patients. Figure shows the survival of all patients in CR at 1 year.

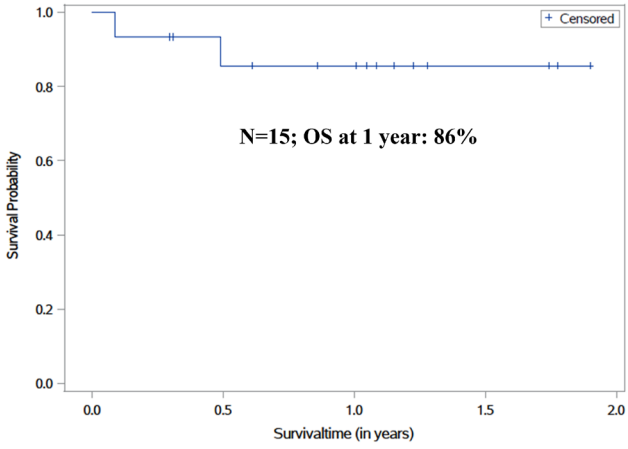

Figure 3. Survival after HCT. Figure shows the overall survival of all patients after HCT.

Hematopoetic cell transplantation (HCT)

Of the 15 patients in CR after induction therapy, including those who discontinued the study prematurely, 14 patients received an allo HCT (two sibling, 12 unrelated donor) and one patient received an autologous transplantation. A fully matched donor was used in seven cases, a haploidentical donor in one case and in three further cases an HLA mismatch was observed in at least one HLA locus. All patients received TBI-based conditioning regimens, 12 Gy TBI and cyclophosphamide ($N=8$), 12 Gy TBI and etoposide ($N=5$), 12 Gy TBI, cyclophosphamide and fludarabine ($N=1$) or 8 Gy TBI and fludarabine ($N=1$). Overall, after a median follow up of 395 days (range 107–693 days) 13 of 15 patients are in continuous complete hematologic remission. Two patients (13%) died of transplant-related infections. All patients had a molecular CR after stem cell transplantation but in five patients (33%) developed molecular relapse median at 187 days (range 110–360) after transplantation. Of the 15 patients 9 received TKI treatment after HCT (60%) and herein 6 patients received IMA and 3 DASA.

Other further therapies after end of study

Twelve of 19 patients (63.1%) completed the study therapy directly after Consolidation I and 10 of 19 (52.5%) received allogeneic HCT without additional chemotherapy.

Two patients received 2 cycles high dose MTX + asparaginase in combination with IMA after regular EOS. In both cases, chemotherapy was given, because HCT was postponed because an appropriate donor was not available. Both patients later received an allo HSCT with an HLA-mismatched donor. Two of the 3 patients with premature study end received FLAG-Ida in combination with IMA. In one case, the additional chemotherapy cycle was given before allo HCT because of persisting high molecular MRD levels. In the other case an autologous HCT was performed, afterwards.

One of the three patients with premature end of study received no consolidation therapy at all. In this patient, various complications such as infections and other toxicities were observed during study treatment. After the EOS the patient received IMA until allo HCT was performed four months after diagnosis.

Discussion

Although the general tolerability of the regimen was acceptable, the early mortality rate of 21% appeared to be unacceptably high for this patient population. Therefore, it is obvious that the study regimen is not recommendable in a larger patient population and the trial was stopped, although the criteria for early discontinuation of the trial because of infeasibility or lack of efficacy were not fulfilled. The reason for the high mortality rate in induction were severe bleeding events and sepsis. With DASA, an enhanced bleeding risk was reported in patients with advanced CML and thrombocytopenia receiving DASA [10]. This could be a compound specific aspect enhancing induction toxicity in combination with intensive chemotherapy. Otherwise no enhanced bleedings were reported in the combination of DASA with Hyper CVAD [4] or low dose intense chemotherapy in elderly patients [6]. Regarding severe infections, it is difficult to distinguish effects of DASA from the general risks of infection during intensive chemotherapy due to neutropenia and mucositis. Same has been reported for the combination of DASA

with Hyper CVAD [4]. A study by Jabbour et al. reported the combination of DASA and Hyper CVAD in front-line therapy of Ph + ALL in a phase II study of 34 patients with untreated Ph + ALL and 7 patients who had received 1 prior cycle of chemotherapy [11]. Thirty-nine patients (95%) achieved CR after the first cycle or were CR at start. Two patients died from infections before response assessment. Twenty-two patients (56%) achieved complete molecular remission (CMR) at a median of 14 weeks from initiation of treatment. Four patients died in CR; 1 from an unrelated cardiac event and 3 from infections. Three patients received an allogeneic stem cell transplant. The median disease free survival was 48 weeks and the median overall survival was 52 weeks [11]. In elderly patients, aged 55 years or more, the addition of DASA to low dose chemotherapy including vincristine, dexamethasone and intermediate dose methotrexate, asparaginase and cytarabine was evaluated in adults with Ph + ALL by the EWALL. Maintenance phase included 6-MP and methotrexate orally as well as dexamethasone. In 30 patients treated at a median age of 71 years, a high CHR rate (96.6%) and a complete molecular remission rate (CMR) after induction of 33% was observed [6]. Seven relapses were associated with the detection of the T315I mutation and one with the F317L. Four patients died while being on study, 4 other patients died from relapse.

The result of this small pilot trial is promising with a molecular negativity rate of 62.5% and an overall survival of 68% at one year. In particular, the molecular response rate is remarkable and compares favorably to results achieved with combination of Blinatumomab and DASA and other combination regimens of DASA and chemotherapy [5, 12]. The high realization rate of HCT is excellent as well as the survival after HCT with 86% at 2 years.

Maintaining the excellent antileukemic efficacy seen in this trial, but improving tolerability, dose reductions of chemotherapy would be a potential option which has been realized in the recently accomplished first-line trial GMALL 08/2013 trial [13]. Internationally, several groups have demonstrated that DASA is able to induce high CR rates and high rates of molecular CR in induction, if only combined with steroids and low intensity chemotherapy [6, 12]. Even if DASA is combined with Blinatumomab for first line treatment, high response rates have been achieved in 61 patients with a molecular remission rate of 24% after induction and combined with a OS rate of 95% at 18 months [12]. Adverse events included infections, neutropenia, pleural effusion and pulmonary hypertension. Mol CR rate in our reported trial was even higher but associated with higher toxicity, as described. In pediatric patients DASA has been shown to improve outcome if used in combination with a standard pediatric chemotherapy approach. This included DASA in combination with daunorubicin cyclophosphamide, vincristine, HD cytarabine, HD methotrexate and L-Asparaginase. Interestingly no severe toxicities were observed when compared compared to IMA [7].

In comparison, in the GMALL-PH01 trial the high molecular remission rate in combination with a high consecutive HCT rate resulted in low relapse rate and no detection of T315I mutations. As described combination of DASA and lower intense chemotherapy resulted in similar high response rates but were far less toxic. It is, however, not clear whether DASA in combination leads to superior results compared to Imatinib. Upcoming results of DASA in combination with immunotherapy are promising but still not standard of care.

The GMALL-PH01 trial shows that full dose chemotherapy in combination with DASA is too toxic to be further pursued. The sweet spot in the further development of treatment of Ph positive Ph+ ALL is to find the right level of treatment to obtain an MRD negative response and whether for durable remission transplant should be pursued or not. More potent TKIs like Ponatinib, having also shown promising efficacy in several trials, should be further evaluated in combination with less toxic chemo- and immunotherapy in order to answer these burning questions.

Summary

This trial shows that first line treatment with DASA in Ph + ALL is a promising strategy. The high molecular CR rates demonstrate high efficacy of DASA. Molecular remission is the most important prerequisite for prevention of relapse, but the questions is which intensity is really needed to reach that goal? The further evaluation of DASA and other TKIs with clearly reduced intensity chemotherapy and or immunotherapy is a promising strategy in current and future trials, but should also address the following questions: which TKI to use best upfront resp. incorporating early TKI switch in case of insufficient molecular response? Do patients with an optimal response need allogeneic SCT for consolidation?

Disclosure statement

The authors declare the following conflict of interest: F.L.: Bristol Myers Squibb, Incyte, and Celgene: consultancy, honoraria; Novartis: consultancy, honoraria, and research

funding. A.V.: Honoraria (Advisory boards, invited talks, consultancy): BMS/Celgene, Delbert, Novartis, Pfizer, SOBI, Travel Support: Amgen. G.K.: Advisory Role or Speaker Honoraria: MSD, Pfizer, Amgen, Novartis, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept. Financing of Scientific Research: BMS-Celgene, Amgen, Abbvie, Eurocept, Medac. C.J.: advisory board: Incyte; research funding from Incyte, received travel support and honoraria from Incyte. A.V.: BMS, Gilead, Novartis, Roche, Abbvie, Astrazeneca, Bejing (Advisory Boards, Invited talks), Roche, Gilead, Janssen (travel grants). B.B.: Honoraria, Consulting or Advisory Role: Amgen, Celgene, Janssen, Kite/Gilead, Miltenyi, MSD, Mundipharma, Noscendo, Novartis, Pfizer, Takeda. Research funding: Astellas, Celgene, Kite/Gilead, MSD, Takeda. H.S.: Honoraria: Novartis, Robert-Bosch-Gesellschaft für Medizinische Forschung, Gilead Sciences, Consulting or Advisory Role: Gilead Sciences, IKP Stuttgart (Robert-Bosch-Gesellschaft für Medizinische Forschung). N.G.: Honoraria (Advisory boards, invited talks): Incyte, Amgen, Novartis, Pfizer; Institutional Funding: Incyte, Amgen, Pfizer. O.O.: advisory roles for Novartis, Ariad, Sanofi Aventis and Bristol-Myers Squibb. Funding by Novartis, Bristol-Myers Squibb and the Deutsche José Carreras Leukämie Stiftung. H.P.: advisory board: Incyte; research funding from Incyte, received travel support and honoraria from Incyte. All other authors declare no competing interests.

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Data availability statement

The trial data set can be obtained upon request to the corresponding author.

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