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Azacitidine in CMML: Matched-pair analyses of daily-life patients reveal modest effects on clinical course and survival ☆☆

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ABSTRACT

Recent data suggest that azacitidine may be beneficial in CMML. We report on 48 CMML-patients treated with azacitidine. Overall response rates were high (70% according to IWG-criteria, including 22% complete responses). Monocyte count and cytogenetics adversely affected survival, whereas age, WHO-type, FAB-type, and spleen size did not. Matched-pair analyses revealed a trend for higher two-year-survival for azacitidine as compared to best supportive care (62% vs. 41%, $p = 0.067$) and longer OS for azacitidine first-line vs. hydroxyurea first-line ($p = 0.072$, median OS 27.7 vs. 6.2 months). This report reinforces existing evidence that azacitidine is safe and efficacious in both myelodysplastic and myeloproliferative CMML.

1. Introduction

Therapy of CMML still remains challenging and unsatisfactory. So far no strategy has proven effective in prolonging overall survival (OS). Allogeneic stem cell transplantation, the only curative option, is only available to a small number of patients, and outcome still remains unsatisfactory, with a disease-free survival of 18–20% at 5 years [1,2]. Until recently, best supportive care (BSC), aimed at ameliorating the symptoms and complications of bone marrow failure, was the mainstay of treatment for CMML. While low-dose cytarabine [3], topotocan [4], farensyltransferase inhibitors [5,6], and oral etoposide [7] have been used in CMML, hydroxyurea is usually the

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Table 1
Comparison of full publications on CMML-patients treated with azacitidine.

Group	Silverman [10]	Fenaux [12]	Costa [13]	van der Helm [17]	Ozbalak [15]	Thorpe [16]	Wong [18]	Fianchi [14]	Ades [19]	Present study
Year published	2002	2009	2011	2011	2012	2012	2012	2012	2013	2013
Country	USA	France	Pennsylvania	Holland	Turkey	Portugal, Australia	Australia	Italy	France, USA	Austria
n	7	9	38 (36)	12	5	10	11	31	76	48
Inhabitants (million)	311.6	65.4	12.8	16.6	74.7	33.2	23.0	60.8	377.0	8.2
n trt. with AZA/capita	0.02	0.14	2.81	0.72	0.07	0.30	0.48	0.51	0.20	5.85
Phase	III	III	Retrosp.	Retrosp.	Retrosp.	Retrosp.	Retrosp.	Retrosp.	Retrosp.	Retrosp.
Median age (years) (range)	n.g.	n.g.	70.5	65 (51–74)	74 (53–80)	66 (41–769	65 (42–80)	69 (53–84)	70 (33–85)	71 (38–87)
Female (%)	n.g.	n.g.	19	50	40	20	n.g.	26	29	41
FAB-subtype (%)										
MD-CMML (<13 G/l)	100	100	31	n.g.	80	60	64	65	57	42
MP-CMML (>13 G/l)	0	0	69	n.g.	20	40	36	35	43	58
WHO-subtype (%)										
CMML-1	n.g.	9	73	n.g.	100	90	64	42	55	40
CMML-2	n.g.	91	27	n.g.	0	10	43	58	45	60
Secondary CMML (%)	n.g.	0	8	n.g.	n.g.	30	n.g.	16	n.g.	8
BM blasts (%)										
<10%	n.g.	0	72	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	60
10–19%	n.g.	100	25	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	40
Unknown	n.g.	0	3	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	0
ECOG > 2 (%)	0	0	n.g.	n.g.	20	n.g.	n.g.	n.g.	n.g.	23
Splenomegaly (%)	n.g.	n.g	28	n.g.	n.g.	40	n.g.	n.g.	30[a]	19[b]
IPSS cytogenetic risk (%)										
Good	n.g.	n.g.	53	58	100	60	55	74	n.g.	73
Intermediate	n.g.	n.g.	36	42	0	20	18	19	n.g.	17
Poor	n.g.	n.g.	8	0	0	20	18	3	n.g.	6
Not evaluable/no data	n.g.	n.g.	3	0	0	0	9	3	n.g.	4
Prior therapy (%)										
None	n.g.	n.g.	44	58	n.g.	40	55	n.g.	53	50
HU	0	n.g.	31	25	n.g.	30	n.g.	35	17	31
G-CSF/ESA	0/allowed	n.g.	8/11	0/0	n.g.	10/10	n.g.	n.g.	12	0/8
Others including CTX	0	n.g.	19	0	n.g.	20	n.g.	n.g.	16	10
Azacitidine schedule (%)										
d1–7	100	100	76	100	100[d]	n.g.	91	90	n.g.	69
d1–5	0	0	24[c]	0	0	n.g.[c]	0	10	n.g.	10
5-2-2	0	0	0	0	0	0	0	0	n.g.	19
Others	0	0	0	0	0	0	9	0	n.g.	2
Median cycles (range)	n.g.	n.g.	5	8 (1–15)	8.5 (8–15)	8 (4–29)	8 (2–29)	6 (2–31)	6 (1–40)	5.5 (1–65)
Median follow-up (months)	n.g.	n.g.	n.g.	n.g.	23	12	15.9	n.g.	36	10
Median OS (months)	n.g.	n.g.	12	n.g.	n.g.	20	17.2	37	29	12.6
ORR (%) (ITT)	n.g.	n.g.	39	50	60	60	55	51	43	54
CR/(m) CR	n.g.	n.g.	11	33	20	40	36	45	25	13
PR	n.g.	n.g.	3	0	20	0	9	3	1	6
HI	n.g.	n.g.	25	17	20	20	9	6	17	35
SD only	n.g.	n.g.	36	33	60	40	36	23	n.g.	8
ORR, *n*/*n* (% ITT)										
MD-CMML	n.g.	n.g.	6/11 (55)	n.g.	2/4 (50)	3/4 (75)	5/7 (71)	n.g.	n.g.	7/20 (35)
MP-CMML	n.g.	n.g.	8/25 (32)	n.g.	1/1 (100)	3/6 (50)	1/4 (25)	n.g.	n.g.	19/28 (68)
ORR, *n*/*n* (% ITT)										
CMML-1	n.g.	n.g.	9/26 (35)	n.g.	3/5 (60)	5/9 (56)	4/7 (57)	n.g.	n.g.	10/18 (56)
CMML-2	n.g.	n.g.	5/9 (56)	n.g.	0/0 (0)	1/1 (100)	2/4 (50)	n.g.	n.g.	15/29 (52)
Prognostic for OS in UVA										
Splenomegaly	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	Yes ($p = 0.02$)	No ($p = 0.435$)[b]
WBC >13 G/l	n.g.	n.g.	Yes ($p = 0.02$)	n.g.	n.g.	n.g.	n.g.	n.g.	Yes ($p = 0.039$)	No ($p = 0.419$)
BM-blasts >10%/CMML-1/-2	n.g.	n.g.	No ($p = 0.3$)	n.g.	n.g.	n.g.	n.g.	n.g.	Yes ($p = 0.05$)	No ($p = 0.636$)

IPSS cytogenetic risk	n.g.	n.g.	Yes ($p = 0.05$)	n.g.	n.g.	n.g.	No (p = n.g.)	No ($p = 0.46$)	No ($p = 0.139$)
Sex	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	No ($p = 0.32$)	No ($p = 0.055$)
Prior trt. excl. growth factors	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	No ($p = 0.07$)	Yes ($p = 0.025$)
Monocytes	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	Yes ($p = 0.05$)[e]	n.g.	Yes ($p = 0.029$)[f]
Overall response	n.g.	n.g.	Yes ($p = 0.04$)	n.g.	n.g.	n.g.	Yes ($p = 0.07$)	n.g.	Yes ($p < 0.001$)
PLT count	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	No (p = n.g.)	n.g.	No ($p = 0.650$)
IPSS	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	No (p = n.g.)	n.g.	No ($p = 0.532$)
AZA dose	n.g.	n.g.	n.g.	n.g.	n.g.	n.g.	No (p = n.g.)	n.g.	No ($p = 0.935$)

trt., treated; MD, myelodysplastic; MP, myeloproliferative; AZA, azacitidine; ORR, overall response rate; ITT, intent to treat; BM, bone marrow; ECOG-PS, European Cooperative Group Prognostic Score; n.g., not given; UVA, univariate analyses.

[a] Palpable splenomegaly.
[b] ≥17 cm.
[c] 100 mg/m^2.
[d] 50 or 75 mg/m^2, maintenance $q = 12$ weeks, treatment cessations with restart at relapse.
[e] ≤/>2 G/l.
[f] ≤/>5 G/l.

treatment of choice for palliative cytoreduction. Although relevant complete response (CR) rates have been observed with intensive chemotherapy, remissions are typically short, even with continuation of intensive post-remission therapy, and longterm disease-free survival remains dismal [4,8,9].

While hypomethylating agents have been prospectively shown to prolong OS in MDS-patients, randomized trials included only 7–14 CMML-patients which were not reported separately [10–12]. Approval of azacitidine in CMML is thus based on limited experience and restricted to non-myeloproliferative disease. Decitabine is not yet approved for the treatment of CMML in Europe. Since FDA-approval, several trials and retrospective reports with azacitidine have included small numbers of CMML patients (Table 1) [10,12–19].

Our aim was to define the value of azacitidine in daily-life patients with CMML in both its myelodysplastic (MD-CMML) and myeloproliferative form (MP-CMML). We thus examined toxicity, efficacy, OS and the effect of putative prognostic parameters on OS in 48 CMML-patients treated with azacitidine (ClinicalTrials.gov: NCT01595295). In the absence of clinical trials comparing hypomethylating agents versus conventional treatment options, it is unclear whether azacitidine can improve overall survival in CMML. We thus performed two matched-pair analyses (i.e. drawing on the data base of the Düsseldorf MDS Registry):: azacitidine versus BSC (42 matched-pairs) and versus hydroxyurea (22 matched-pairs).

2. Methods

Registry design, patient eligibility, data collection and monitoring, assessment of efficacy, safety and endpoints within the Austrian Azacitidine registry were performed as previously described [20]. OS was assessed using the Kaplan–Meier method. Univariate analyses were performed with log-rank tests. Cox-regression stratified on the various factors was used for analyses of risk-factors for OS. Baseline characteristics were compared by non-parametric tests (Chi-squared test for qualitative variables, Wilcoxson test for quantitative variables). Survival rates at 1 and 2 years were compared using the z-test for proportions. Analyses were performed with SAS and/or SPSS. The search-pool for matched-pairs comprised 516 CMML-patients: 426 CMML-patients from the Düsseldorf MDS Registry, and 90 CMML-patients from Austrian hematology centers. Matching was performed as previously described [21]. The following characteristics were used for matching: age (±5 years), gender, CMML-type according to WHO-classification (CMML-1/2) as well as FAB-classification (MD-/MP-CMML). In cases in which several potential matched-pair partners were possible, the most appropriate partner was chosen based on parity with IPSS cytogenetic risk category and/or score, LDH </≥225 mg/dl and spleen size. 42 BSC-matches and 22 hydroxyurea-matches were found. Main difficulties were finding matches for young, female CMML-1 patients and for MD-CMML patients treated with hydroxyurea. These bottlenecks are comprehensible, since CMML predominantly occurs in males, and young patients with MD-CMML are rarely treated with BSC or hydroxyurea only. Survival was measured from initial diagnosis for the matched-pair analysis with BSC, and from onset of treatment with azacitidine or hydroxyurea for the matched-pair analysis with hydroxyurea. Treatment choice, time of treatment initiation, duration and modification were exclusively at the discretion of the respective treating physician.

3. Results

3.1. Patient characteristics

Between 02/2009 and 02/2013, 48 CMML-patients from 11 centers for hematology and oncology were included; no patients were excluded from the analyses. Patient baseline characteristics are shown in Table 2. Median age was 71 years (range 38–87), 60% had CMML-2, 42% had MD-CMML, and 8% had treatment-related CMML. Splenomegaly at azacitidine treatment start was present in 48% of patients. According to the CMML-specific cytogenetic score (CPSS) [22], 71%, 8% and 17% had a good, intermediate or unfavorable karyotype, respectively (Table 2). Off-EMA-label use of azacitidine occurred in 77% (i.e. patients with CMML-1 and/or MP-CMML).

Table 2
Baseline characteristics.

Median age (years) (range)	71 (38–87)
Gender male, *n* (%)	29 (60.4)
WHO-subtype, *n* (%)	
CMML-1	19 (39.6)
CMML-2	29 (60.4)
CMML type, *n* (%)	
De novo CMML	44 (91.7)
Treatment-related CMML	4 (8.3)
FAB-subtype, *n* (%)	
MD-CMML	20 (41.7)
MP-CMML	28 (58.3)
Splenomegaly	
Yes	23 (47.9)
≥17 < 20 cm	6 (12.5)
≥20 cm	3 (6.3)
No	23 (47.9)
Unknown	2 (4.2)
PB blasts, *n* (%)	
0%	15 (31.3)
>0%	33 (68.8)
BM blasts, *n* (%)	
<10%	29 (60.4)
10–19%	19 (39.6)
Cytopenias at diagnosis, *n* (%)	
1 Cytopenia	16 (33.3)
2 Cytopenias	29 (60.4)
3 Cytopenias	3 (6.3)
Transfusion dependence (TD) prior to AZA, *n* (%)	
Any type of TD	29 (60.4)
RBC-TD	24 (50.0)
PLT-TD	12 (25.0)
RBC-TD + PLT-TD	7 (14.6)
FAB-subtype and RBC-TD, *n*/*n* (%)	
MD-CMML	10/20 (50.0)
MP-CMML	14/28 (50.0)
FAB-subtype and PLT-TD, *n*/*n* (%)	
MD-CMML	5/20 (25.0)
MP-CMML	7/28 (25.0)
Serum-erythropoietin, *n* (%)	
<50 IU/l	12 (25.0)
50–500	9 (18.8)
>500	0 (0.0)
Not evaluated	27 (56.3)
LDH, *n* (%)	
<225 U/l	9 (19.2)
>225 U/l	35 (72.9)
Not evaluated	4 (8.5)
Ferritin, *n* (%)	
<1000 μg/l	16 (33.3)
≥1000 μg/l	8 (17.0)
Not evaluated	24 (51.1)
Pre-treatment cytogenetics, *n* (%)[a,b]	
Not evaluable/no data	2 (4.2)
Normal	33 (68.8)
Specific aberrations	13 (27.1)
+8, −7	7 (14.6), 2 (4.2)
Others, complex	3 (6.3)
IPSS cytogenetic risk group, *n* (%)	
Good	35 (72.9)
Intermediate	8 (16.7)
Poor	3 (6.3)
Not evaluable/no data	2 (4.2)
CMML cytogenetic risk group, *n* (%)	
Low	30 (70.8)
Intermediate	4 (8.3)
High	8 (16.7)
Not evaluable/no data	2 (4.2)
Comorbidities, *n* (%)[a]	
None	7 (14.6)
Thromboembolic episodes	1 (2.1)
Renal insufficiency	15 (31.3)
Liver disease	10 (20.8)
Diabetes mellitus	8 (16.7)
Coronary artery disease	11 (22.9)
COPD	7 (14.6)
Solid tumor	4 (8.3)
Hematologic neoplasia + MGUS	7 (14.6)
Number of comorbidities, *n* (%)	
0–1	15 (31.3)
2–3	19 (39.6)
>3	14 (29.2)
ECOG-PS, *n* (%)	
ECOG <2	37 (77.1)
ECOG >2	11 (22.9)
HCT-CI, *n* (%)	
Low risk	10 (20.8)
Int risk	19 (39.6)
High risk	19 (39.6)
Treatment prior to azacitidine, *n* (%)[a]	
None	26 (54.2)
Erythropoiesis stimulating agents (ESA)	4 (8.3)
Thrombopoiesis stimulating agents (TSA)	1 (2.1)
Iron chelation treatment (ICT)	4 (8.3)
Hydroxyurea (HU)	15 (31.3)
Chemotherapy (CTX)	2 (4.2)
Others	3 (6.3)
Reason for treatment, *n* (%)[a]	
1st line treatment	26 (54.2)
Bridging to allogeneic-SCT	2 (4.2)
Maintenance after CR to chemotherapy	1 (2.1)
No CR to conventional chemotherapy/allogeneic-SCT	1 (2.1)
No CR/adequate disease control to other prior HU	15 (31.3)
No CR/adequate disease control to other drugs	4 (8.3)

MD, myelodysplastic CMML (i.e. CMML with <13 G/l WBC); MP, myeloproliferative (i.e. CMML with <13 G/l WBC); PB, peripheral blood; BM, bone marrow; RBC, red blood cell; PLT, platelet; COPD, chronic obstructive pulmonary disease; MGUS, monoclonal gammopathy of unknown significance; ECOG-PS, European Cooperative Group Prognostic Score; HCT-CI, Hematopoietic Stem Cell Comorbidity Index; SCT, stem cell transplantation; CR, complete response.

[a] Numbers may add up to >100% as multiple selections were possible.

[b] Pre-treatment cytogenetics were available in 94% of patients and were determined by conventional metaphase karyotyping, interphase-FISH, or both.

3.2. Treatment modalities

A total of 458 azacitidine cycles were applied to all patients. Azacitidine was given 1st line (54%), after hydroxyurea/chemotherapy-failure (33%), or after prior growth-factors/iron-chelators/other substances (13%) (Table 2). The median number of azacitidine cycles was 5.5 (range 1–65). Most patients (88%) predominantly received 7 days of azacitidine (69% FDA-approved d1–7, 19% 5-2-2) (Supplemental Table 1). FDA-approved azacitidine target-dose (75 mg/m^2 × 7 ± 10%) was reached in 62% of applied cycles; 18% of all cycles were administered as 'flat' dosage (i.e. 100 mg azacitidine/cycle-day). Dose reduction of azacitidine due to an adverse event was necessary in 17%.

3.3. Concomitant treatment and best supportive care measures

Erythropoietin stimulating agents (ESA) (9%), iron chelation treatment (4%), and G-CSF (3%) were given in parallel to azacitidine when deemed necessary by the treating physician. Nine patients, five of which had already received hydroxyurea prior to azacitidine treatment start, received hydroxyurea concomitantly.

3.4. Overall response to azacitidine

Overall response (defined according to IWG 2006 criteria [23] and including complete response (CR), marrow response (mCR), partial response (PR) and/or hematologic improvement (HI)) was documented in 54.2% of the intention-to-treat (ITT) cohort and in 70.3% of patients evaluable according to IWG-criteria (i.e. had received >2 cycles of azacitidine); Hematologic improvement was documented in 50% (ITT) and 65% (IWG), respectively; CR/mCR was achieved in 13% (ITT) and 26% (IWG) (Supplemental Table 2).

Response to azacitidine did not correlate with the schedule applied (i.e. 5 or 7 days), or azacitidine dose/cycle (Supplemental Table 3). The median number of cycles received by responding patients was 10.5 (range 3–65), as compared to 2.5 (range 1–18) for non-responders.

Overall response rate was not lower for patient populations for whom azacitidine has not been approved by EMA in Europe yet: 67% for CMML-1 and 83% for MP-CMML (Supplemental Table 2).

3.5. Time to best response and response deepening

Median time to first response was 4.0 months. First response occurred at cycle 3, 4 and 5 in 42%, 77% and 92% of responding patients, respectively. First response was best response in 81% of responding patients. Further deepening of response after first response (i.e. marrow response occurring after HI) was seen in 19% of responders. Median time from first to best response was 3.5 months.

3.6. Toxicity and adverse events

A total of 195 adverse events (AE) were documented in 456 azacitidine cycles. The number of AE was highest in cycles one and two. Overall, 29% of all AE and 33% of grade 3–4 (G3–4) AE were attributed to azacitidine; 22% resulted in hospitalization, 5% resulted in death; 68% had no consequence for azacitidine treatment. AE resulted in azacitidine treatment pause, dose reduction, prolongation of azacitidine cycle duration >28 days, or termination of treatment in 17%, 6%, 3% and 8%, respectively (Supplemental Table 4).

G3–4 hematologic toxicity occurred in 56% (Table 3). Clinically relevant bleeding events were noted in 31%. G3–4 infectious events occurred in 17% and were dominated by pulmonary infections, HSV- and CMV-reactivations.

Non-hematologic G3–4 events mostly occurred as injection site reactions (10%) and in the cardiac system (21%) (Table 3). In 70% of patients experiencing cardiac G3–4 events, pre-existing coronary artery disease ($n = 4$), arrhythmias ($n = 5$) and/or valvular heart disease ($n = 3$) were documented prior to azacitidine treatment and worsening was not thought to be azacitidine-related.

3.7. Overall survival and evaluation of potential prognostic parameters

At the time of data cut-off (11.03.2013), 34 patients were dead, eight were alive and still on azacitidine, and six were alive, but treatment with azacitidine was terminated. No patients were lost to follow-up. Median follow-up was 9.8 months.

Median OS was 31.2 (95% CI 26.1–36.6) months as of first diagnosis, and 12.6 (95% CI 6.3–18.9) months as of treatment start with azacitidine. Median time from initial diagnosis to initiation of azacitidine was 0.9 months for untreated ($n = 26$), 14.7 months for pretreated ($n = 22$) and 7.4 months for the total cohort, respectively. Termination of azacitidine treatment in the eleven patients that received ≤2 cycles was death ($n = 6$), disease progression ($n = 3$), toxicity ($n = 1$) and patient's wish ($n = 1$), respectively. Median time from azacitidine treatment stop to death was 2.1 months.

Median OS as of azacitidine treatment start in responding patients was 19.4 (95% CI 7.9–17.4; range 2.2–68.2) months. Progression free survival (PFS) in responding patients was 12.6 (95% CI 13.1–28.8; range −1.5–68.2) months. Progression defining events were death due to any reason ($n = 10$), disease relapse/progression after HI ($n = 7$), new transfusion dependence ($n = 2$), transformation to AML ($n = 2$), allogeneic stem cell transplantation ($n = 1$), and no event/still on AZA at cut-off date ($n = 4$), respectively.

Table 3
Specific adverse events.

Variable	Grade	*n* pts. (%)	*n* total events
Hematologic toxicity[a]	G3–4	27 (56.3)	73
Thrombopenia	G3–4	21 (43.8)	59
Neutropenia	G3–4	10 (20.8)	12
Anemia	G3–4	19 (39.6)	47
Bleeding events	–	15 (31.3)	29
Febrile neutropenia	–	6 (12.5)	7
Infectious	G1–2	17 (35.4)	55
complications	G3–4	8 (16.7)	11
Non-hematologic toxicity			
Liver	G1–2	0 (0.0)	0
	G3–4	0 (0.0)	0
Kidney	G1–2	4 (8.3)	5
	G3–4	0 (0.0)	0
Heart[b]	G1–2	2 (4.2)	3
	G3–4	8 (16.7)	14
Blood pressure	G1–2	0 (0.0)	0
	G3–4	0 (0.0)	0
Metabolic	G1–2	2 (4.2)	2
	G3–4	0 (0.0)	0
Thromboembolic	G1–2	2 (4.2)	2
	G3–4	1 (2.1)	1
Neurologic	G1–2	6 (12.5)	10
	G3–4	1 (2.1)	1
Nausea	G1–2	4 (8.3)	4
	G3–4	0 (0.0)	0
Vomiting	G1–2	1 (2.1)	1
	G3–4	0 (0.0)	0
Constipation	G1–2	3 (6.3)	5
	G3–4	0 (0.0)	0
Diarrhea	G1–2	6 (12.5)	9
	G3–4	0 (0.0)	0
GIT-others	G1–2	5 (10.4)	5
	G3–4	0 (0.0)	0
Injection site	G1–2	9 (18.8)	12
reaction	G3–4	5 (10.4)	8
Fatigue	Relieved by rest	6 (12.5)	7
	Not relieved by rest	8 (16.7)	11
	Limiting self care	1 (2.1)	1
Pain	Mild	9 (18.8)	18
	Moderate	7 (14.6)	11
	Severe	0 (0.0)	0
Surgery	Elective	3 (6.3)	4
	Emergency	3 (6.3)	3
Fall	Total	8 (16.7)	10
	With fracture	1 (2.1)	1
	With hemorrhage	2 (4.2)	2
Novel solid tumor	Yes	0 (0.0)	0

Pts., patients; GIT, gastrointestinal.

[a] Grade 3–4 cytopenias reported, are those that were documented as adverse events, and thus felt to be a worsening of pre-existing cytopenia by the respective treating physicians.

[b] Reported cardiac AE were: left-ventricular output failure ($n = 12$ events in 6 patients), arrhythmia ($n = 2$), cardiac ischemia ($n = 3$), sudden cardiac death ($n = 1$), and valvular insufficiency ($n = 1$).

In univariate analysis the following baseline parameters had a significant adverse effect on overall survival: pretreatment with hydroxyurea ($p = 0.011$), monocyte count >5000/μl ($p = 0.029$), and adverse cytogenetics (−7, −7*q*, abn(3*q*), or complex karyotype) ($p = 0.027$). Addition of trisomy 8 as adverse cytogenetic marker (as defined by the CMML-specific cytogenetic risk group [22]) did not add impact, but rather resulted in loss of statistical significance (Fig. 1 and Supplemental Table 3).

Female gender had a trend for an effect on OS ($p = 0.055$, Supplemental Table 3). A trend for worse OS was seen in patients with red blood cell transfusion dependence (RBC-TD) prior to azacitidine treatment start ($p = 0.068$).

Baseline factors that did not significantly affect OS included age </≥75, WHO-type, FAB-type, bone marrow blast count <10%/10–20%, spleen size </≥17 cm, peripheral blood blasts,

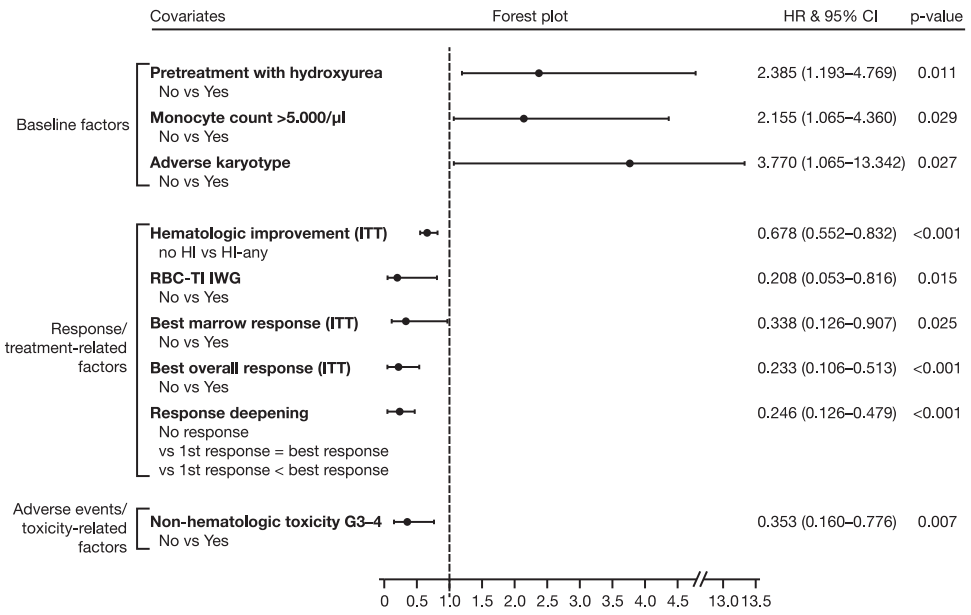

Fig. 1. Forrest plot of factors significantly affecting overall survival of azacitidine treated CMML-patients ($n = 48$) in univariate analyses. HI indicates hematologic improvement; RBC-TI, red blood cell transfusion independence; IWG, International Working Group Criteria; ITT, intent to treat population; Adverse karyotype was defined as presence of −7q, −7 and/or complex karyotype.

neutrophil count </≥2000/μl, lymphocyte count </≥2000/μl, platelet-TD, S-EPO level, prior treatment with ESA or with ESA/G-CSF/iron chelators, LDH ≤/>225 IU/l, ECOG-PS, HCT-CI and the absolute number of comorbidities. Neither the IPSS cytogenetic risk score, nor grouping according to the IPSS, R-IPSS, R-IPSS-age, WPSS, APSS or the CPSS risk scoring systems could prognosticate OS (Supplemental Table 3). No significant effect on OS could be detected for achievement of FDA-approved azacitidine dose or schedule, or treatment on/off-label according to EMA-label. Concomitant hydroxyurea had no influence on OS (Supplemental Table 3).

The following response related factors had a significant effect on overall survival: achievement of RBC transfusion independence (RBC-TI) ($p = 0.015$), hematologic improvement ($p < 0.001$), marrow response ($p = 0.025$), and overall response ($p < 0.0001$) (Fig. 1). Responders had significantly longer OS than non-responders (19.4 vs. 5.6 months, $p < 0.001$), irrespective of CMML-subgroup according to WHO- or FAB-classification, or whether patients were treated off-label according to EMA (Supplemental Table 5). Continued azacitidine beyond first response resulted in further deepening of response in 19% of responders. This translated into significantly longer OS, compared with patients for whom first response was best response (32.8 vs. 17.0 months, $p < 0.001$) (Fig. 1).

The only adverse event and toxicity-related factor that had a significant negative effect on OS was non-hematologic toxicity G3–4 ($p = 0.007$) (Fig. 1). It made no difference whether occurring G3–4 adverse events were attributable to azacitidine or not (Supplemental Table 3).

3.8. Matched-pair analyses reveal modest effects of azacitidine on survival in CMML

Patient characteristics of parameters used for pairing of matches for all cohorts can be taken from Supplemental Table 6. Median OS of azacitidine vs. BSC was 31.2 vs. 17.0 months, respectively ($p = 0.251$) (Supplemental Figure 1A). No statistically significant difference in OS could be found in any of the subgroup-analyses (azacitidine 1st-line, azacitidine after hydroxyurea/chemotherapy-failure, MD-CMML, MP-CMML, treatment on/off-EMA-label). However, OS was consistently longer and OS-differences of plus 7.8–18.0 months for the azacitidine-treated cohorts as compared to the BSC-cohorts were observed (Supplemental Figure 1B and C and Supplemental Table 7). In addition, a trend for higher two-year-survival was observed for the total azacitidine vs. BSC cohort (62% vs. 41%, $p = 0.067$), as well as for the myelodysplastic subgroup (79% vs. 54%, $p = 0.085$) and CMML-patients treated off-EMA-label (60% vs. 38%, $p = 0.099$) (Supplemental Table 7).

Matched-pair analysis of azacitidine vs. hydroxyurea revealed no difference in median OS as of treatment start (7.5 vs. 6.2 months ($p = 0.251$); Supplemental Figure 1D, and Supplemental Table 7) or as of initial diagnosis (18.3 vs. 17.0 months ($p = 0.722$); Supplemental Figure 2). However, comparison of azacitidine 1st-line vs. hydroxyurea 1st-line revealed a trend for longer OS as of treatment start in the azacitidine-cohort despite small sample sizes (median OS 27.7 vs. 6.2 months, $p = 0.072$) (Fig. 2 and Supplemental Table 7).

4. Discussion

In the absence of clinical trials performed exclusively in CMML-patients, it is currently unclear whether azacitidine can improve OS in CMML. We here report on 48 Austrian CMML-patients who were treated with azacitidine and were collected in the recently established Austrian Azacitidine Registry.

The overall response rate (ITT) observed in the present study (54%) is similar to that documented in previous reports (39–60%). However, median OS was relatively low in our patients (12.6 months), which may be due to the large number of pretreated patients (46%). Responders had a median OS of 19.4 months and a median PFS of 12.6 months. Short PFS is likely due to a high rate of deaths not considered to be disease- or treatment-related (70% of PFS defining death events): cardiac failure (5/10 of death events), renal failure, cerebral hemorrhage, and fall with fracture and ensuing death. In addition, 8/26 responders had hematologic improvement in one cell lineage only. Five of these had a response in the white blood cell compartment only, reflecting palliative cytoreduction, and all of these had very short PFS (range 2.2–8.7 months).

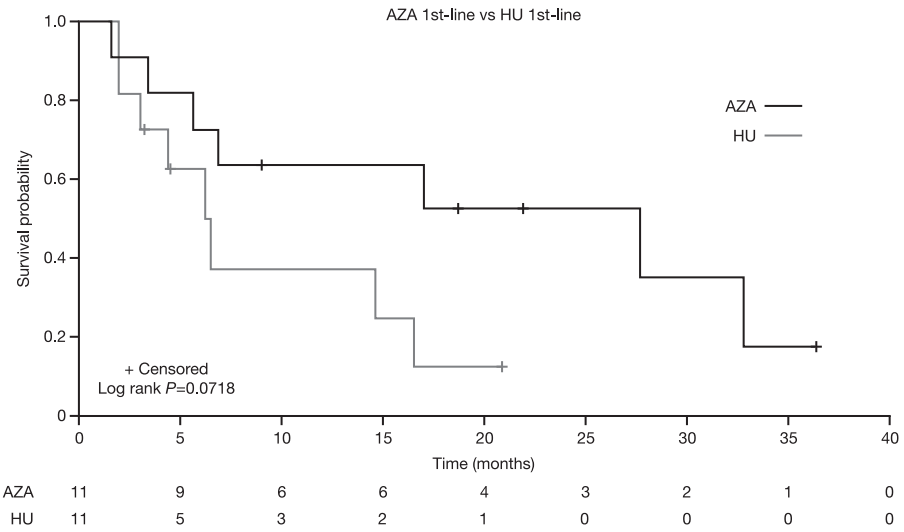

Fig. 2. Kaplan–Meier curve of matched-pair analysis: Azacitidine 1st line vs. hydroxyurea 1st-line. Median overall survival was 27.7 in the azacitidine treated cohort vs. 6.2 months for the hydroxyurea treated cohort ($p = 0.072$).

Our results suggest that some CMML-patients may benefit from azacitidine treatment, irrespective of the WHO- or FAB-classification, and irrespective of whether they were treated according to EMA-label for azacitidine or not (Supplemental Tables 2 and 5). Others have also shown relevant responses to azacitidine in non-EMA-indication cohorts (Table 1). Not surprisingly, responders always had longer OS than non-responders Therefore, in our opinion, MP-CMML and/or CMML-1 patients requiring treatment, i.e. constitutive symptoms due to hyperproliferation and/or splenomegaly and/or transfusion dependence, should not be precluded from treatment with azacitidine.

Baseline markers that predict response to azacitidine would be desirable, as non-responding patients may fare identically with BSC and/or palliative hydroxyurea treatment only. The knowledge on predictive baseline markers for hypomethylating agents is at best descriptive for CMML-patients treated with azacitidine, and conflicting results exist for most variables, which is likely due to small patient numbers (Table 1). We analyzed a number of risk factors known to be relevant in CMML (Table 1 and Supplemental Table 3). In these analyses, we show that treatment with hydroxyurea prior to azacitidine may adversely affect OS (median OS 7.9 vs. 16.9 months, $p = 0.011$). Similarly, Ades et al. showed a trend ($p = 0.07$) for worse OS for patients pre-treated with either hydroxyurea ($n = 13$) or chemotherapy ($n = 12$), but did not report on the effect of pretreatment with hydroxyurea alone [19]. Comparing our results with those of fully published CMML-cohorts treated with azacitidine, it seems as if elevated monocyte count is the only baseline variable which consistently adversely affected OS, IPSS-score, PLT-count, and azacitidine dose do not seem to affect OS, whereas conflicting results exist for all other parameters examined (Table 1) [10,12–19].

In the past, CMML patients were often risk assessed with prognostic scoring systems developed for MDS, i.e. the IPSS [24]. Several prognostic scores have been developed for CMML [22,24–29]. However, currently there is no agreement on prognostic factors or a prognostic score for CMML [30]. We analyzed IPSS, R-IPSS, R-IPSS-age, WPSS, APSS and CPSS, none of which could sufficiently separate survival curves in our large cohort of azacitidine treated CMML-patients (Supplemental Table 3). Our data therefore confirm the ongoing need for an adequate risk-assessment tool in CMML, the absence of which, likely reflects the immense tumor heterogeneity and multiple molecular abnormalities observed in CMML [30,31]. Recent insights indicate mutations in TET2 and ASXL1 genes, -both of which occur frequently in CMML-, as initial driver mutations thought to play a relevant role in the etiopathogenesis of the disease [32]. Conflicting data exist as to whether the incorporation of ASXL1 and/or TET2 mutation status improves the prediction of outcome compared with scores based on clinical parameters only [33,34].

In our CMML-cohort neither response to azacitidine, nor overall survival correlated with achievement of the FDA-approved target dose, the cumulative dose received per cycle, or the predominantly applied schedule, similar to our observations in AML [20]. Others [14] have found similar results, corroborating the impression of non-inferiority of alternative schedules and dosages demonstrated by our data.

Special emphasis was placed on documentation of adverse events in quality and quantity similar to that of clinical trials. We present here, the first comprehensive toxicity and adverse events evaluation for azacitidine treated CMML-patients (Table 3). Importantly, occurrence of AE per se, as well as dose reductions of azacitidine resulting there from, did not negatively impact OS (Supplemental Table 3). Rare cases of non-hematologic G3–4 events, occurring mainly in the cardiac system in patients with preexisting cardiac disease, were the only AE to adversely affect OS (Fig. 1). We recently reported similar safety results for 155 AML-patients [20]. In our opinion, the occurrence of AE should not lead to permanent treatment discontinuation in most cases, and azacitidine treatment should be continued as planned whenever possible, if necessary with dose reduction and/or treatment pause.

This represents the first matched-pair analysis of azacitidine treated CMML-patients. In the comparison of azacitidine vs. BSC median OS was consistently longer and survival differences of up to 21.5 months were observed (Supplemental Figure 1A–C and Supplemental Table 6). Kaplan–Meier curves separated nicely initially but converged at ~50 months (Supplemental Figure 1A and B). Trends for higher two-year-survival were observed for the total azacitidine vs. BSC cohort (62% vs. 41%, $p = 0.067$), the myelodysplastic subgroup (79% vs. 54%, $p = 0.085$), and the off-EMA-label subgroup (60% vs. 38%, $p = 0.099$). Although statistical significance was not reached, these results may be clinically relevant.

We also performed a matched-pair analysis of azacitidine-treated patients with hydroxyurea-treated patients. We chose hydroxyurea as treatment comparator as the only phase-III trial performed exclusively in CMML-patients (performed 17 years ago) demonstrated superiority of hydroxyurea ($n = 53$) over etoposid

($n = 52$) [35]. In our matched-pair analysis, median OS differences for azacitidine vs. hydroxyurea were low (7.5 vs. 6.2 months) and did not reach statistical significance (Supplemental Figure 1D). Fifteen patients were pretreated with hydroxyurea prior to azacitidine, and this was a negative predictor of OS for patients subsequently treated with azacitidine ($p = 0.011$, median OS 7.9 vs. 16.9 months) (Fig. 1). We thus analyzed treatment-naive and hydroxyurea/chemotherapy-pretreated matched-pair cohorts separately. Comparison of azacitidine 1st-line vs. hydroxyurea 1st-line revealed a trend for longer OS in the azacitidine-cohort ($p = 0.072$, median OS 27.7 vs. 6.2 months) (Fig. 2 and Supplemental Table 6). In order to improve the impact of our findings, larger patient numbers will be required to be able to draw definite conclusions. However, the rarity of the disease, the widespread use of azacitidine in CMML, as well as the lack of other approved substances in this indication will be limiting factors in reaching sufficiently large patient numbers. In this regard, an international randomized trial comparing front-line azacitidine with frontline hydroxyurea would be highly desirable (especially in MP-CMML). Pulsed high-dose hydroxyurea (2–3 g every 8 h for 48 h at intervals of 1–4 weeks) as comparator would be an interesting concept [36–38].

Our 48 patient datasets represent a larger number of cases than most existing published clinical trial data. This report reinforces existing evidence that azacitidine can be safely applied, is efficacious, and may be a new forthcoming standard of treatment in both myelodysplastic and myeloproliferative CMML. Bearing the inherent limitations of data generated from registries, as well as the (in statistical terms) rather small patient number in mind, our observations of trends for survival differences of up to 21.5 months seem encouraging, and we cautiously hypothesize, that azacitidine may result in longer OS of CMML-patients when used as 1st-line treatment. CMML-patients refractory to hydroxyurea and or chemotherapy do not seem to profit from azacitidine therapy and may fare identically with BSC and/or palliative cytoreduction with hydroxyurea. A large randomized trial is urgently needed to identify in which conditions hypomethylating agents may be useful in CMML.

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Conflict of interest statement

Consultant or advisory role: LP, Celgene, Bristol-Myers Squibb, Novartis; WS, Celgene; SB, Celgene; MP, Celgene, Novartis; MG, Mundipharma; AL, Celgene; RS, Celgene; PV, Novartis, BMS, Celgene; RG, Bristol-Myers-Squibb, Cephalon, Celgene.

Honoraria: LP, Celgene, Bristol-Myers Squibb, Novartis, AOP Orphan Pharmaceuticals; UG, Celgene, Janssen; WS, Celgene, Novartis; SB, Mundipharma, Novartis, AOP Orphan Pharmaceuticals; MP, Celgene, Novartis, Janssen-Cilag; MG, Pfizer, Mundipharma; RS, Ratiopharm, Celgene; PV, BMS; RG, Amgen, Eisai, Mundipharma, Merck, Janssen-Cilag, Genentech, Novartis, Astra-Zeneca, Cephalon, Boehringer-Ingelheim, Pfizer, Roche, Bristol-Myers Squibb, Sanofi Aventis.

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Authors' contributions. All authors had access to all the clinical data, and were kept up-to date with recent results of the registry via oral presentations from LP at regular intervals. All authors participated in regular critical discussions concerning the status and direction of the registry as well as the data to be published. All authors had the opportunity to review the final manuscript prior to submission. The primary and corresponding authors had final responsibility for the decision to submit for publication. *Conception and design:* LP and RG; *Statistics and online CRF:* LP; *Collection and assembly of data:* all authors; *Data analysis and interpretation:* Lisa Pleyer, Richard Greil; *Manuscript writing:* LP; *Critical revision and final approval of the manuscript:* all authors; Provision of patients: all authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2014.01.006.

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