



Early Release Paper

Transfusion independence and survival in patients with acute myeloid leukemia treated with 5-azacytidine

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Haematologica 2012 [Epub ahead of print]

Citation: Gavillet M, Noetzli J, Blum S, Duchosal MA, Spertini O, and Lambert JF. Transfusion independence and survival in patients with acute myeloid leukemia treated with 5-azacytidine. *Haematologica*. 2012; 97:xxx
doi:10.3324/haematol.2012.065151

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Transfusion independence and survival in patients with acute myeloid leukemia treated with 5-azacytidine

Reanalysis of the CALGB (1) and AZA001 (2) studies in advanced myelodysplastic syndrome (MDS) suggests that 5-azacytidine (AZA) is effective for acute myeloblastic leukemia (AML) with <30% bone marrow blasts. Most AML patients are elderly (>65 years old) and unfit for intensive chemotherapy and allogeneic transplantation (3); prognosis is dreadful with median survival of a few months (4). For these patients appropriate treatments are best supportive care or low dose cytarabine (3). Compared with best supportive care, low-dose cytarabine more frequently induces complete remissions (18% vs 1%) and prolongs survival (3.8 vs 2.5 months) (3). AZA targets DNA methyltransferase and reactivates quiescent genes (5), decreases leukemic cell proliferation and induces cell differentiation. In higher risk MDS or in AML with <30% bone marrow blasts (6), AZA outperformed conventional care (best supportive care, low-dose cytarabine, and intensive chemotherapy) (7) with longer hematologic improvement and transfusion independence (TI) (5). Here, we postulated that patients unfit for standard AML chemotherapy might also benefit from AZA, irrespectively of bone marrow blast count.

We systematically reviewed charts of all patients treated with AZA at our institution between January 1st 2007 and December 31st 2011, and identified 52 consecutive AML patients. These patients were not eligible for intensive chemotherapy due to advanced age (n=33) or comorbidities (n=9), or were refractory to initial intensive chemotherapy (n=10). AZA was administered at 100mg/m² sc day 1-5, over 28-day cycles. This schedule is equivalent to standard day 1-7 MDS treatment (8) and allows weekday outpatient treatment (2). Therapy was continued until disease progression, as survival benefit is extended beyond achievement of best response (9). Indication for transfusion was based on symptoms, comorbidities, and laboratory values (generally Hb<80g/l and PLT<10G/l). Transfusion independence was defined as ≥8 weeks without red blood cell (RBC-TI) and/or platelet (PLT-TI) transfusion (1, 7). The indication to treat patients with baseline RBC-TI was based on appearance of agranulocytosis (n=3), high peripheral blood or marrow blast counts (n=5), and/or AML relapse (n=1). Overall survival (OS) was measured from the first administration

of AZA to death. Five surviving patients were censored on December 31th 2011. The median follow-up of censored patients was 12.2 months. Statistical analysis was performed using Stata software (Statacorp LP, College Station, Texas, USA).

At baseline, 15% (n=9) of our patients had RBC-TI and 25% (n=13) PLT-TI. Median overall survival of the 52 enrolled patients was 8.6 months and 12-month survival rate was 28% [95CI 15-43%]. We excluded 14 patients from transfusion and survival analyses, since they did not reach the minimal 8-week observation period. Among them, 11 patients received only 1 cycle of AZA and 3 received 2 cycles. Treatment was interrupted due to premature death or disease progression (n=12), or availability of a donor for allogeneic stem cell transplantation (n=2). Among these 14 patients, 3 had RBC-TI and 3 had PLT-TI at the onset of therapy. Median OS was 1.3 months [0.5-23.7].

Characteristics of the 38 remaining patients are presented in Table 1. Patients with baseline or acquired RBC-TI (n=22) were grouped and compared to patients that never reached RBC-TI (n=16). Among patients with transfusion independence, 6 had RBC-TI at baseline while 16 achieved RBC-TI under therapy. Except for age, which was older for patients with RBC-TI, we found no differences in baseline characteristics. Our 38 patients received a median of 6 [3-20] cycles of AZA. Overall response rate was 23% (n=9), distributed in 7 complete response with incomplete blood count recovery (CRi) and 2 partial remission (PR) (10). The residual 29 patients exhibited resistant disease (RD, 76%). RD status was equally distributed among transfusion independent and transfusion dependent groups (13 vs 16).

RBC-TI at baseline or under AZA therapy (n=22) was associated to prolonged survival. The median OS of transfusion independent patients was 11.1 months vs. 5.0 months for transfusion dependent patients (12-month OS 40% [95CI 19-60%] vs. 13% [95CI 2-32%], P=0.0006, Figure 1A). Presence of transfusion independence at baseline (n=6) or its achievement under treatment (n=16) had similar survival outcome (median OS 10.7 vs. 11.9, 12-month OS 40% [95CI 17-63%] vs. 45% [95CI 5-75%], P=NS, Figure 1B). Median OS of transfusion dependent patients reported here (5.0 months) is similar to that observed for patients enrolled in AML14 trial who received best supportive care (2.5 months) or low-dose cytarabine (3.8 months) (3). The impact of PLT-TI on survival was similar, although not significant (OS 10.7 vs.

5.4 months, 12-month OS 32% [95CI 14-52%] vs. 21% [95CI 5-45%], P=0.053). The median delay to reach RBC-TI or PLT-TI after therapy initiation was 85 days [60-143] and 73 days [35-154], respectively (~3 AZA cycles). As observed in MDS patients (1), transfusion independence was achieved in all responding patients by the end of the 6th cycle. In patients with baseline RBC-TI, the median duration of transfusion independence was 22 weeks [8 to 42]. When obtained in response to AZA, the median duration of transfusion independence reached 30 weeks [10 to 88]. In our country, blood product expenses in transfusion dependent patients (median 5 RBC and 6 PLT transfusions per month for our collective) were comparable to those of continued AZA therapy in transfusion independent patients.

Univariate analysis of survival showed significant differences for peripheral blood blast count $\geq 20\%$, relapsed/refractory disease, baseline PLT-TI and, baseline or acquired RBC-TI. Interestingly, BM blast level was not predictive of survival or response to treatment. In multivariate analysis, baseline or acquired RBC-TI remained the single parameter favorably affecting survival (HR 0.36 [95CI 0.16-0.77], P=0.009).

In conclusion, we report here for the first time that AZA can induce transfusion independence in half of previously transfusion dependent patients and that transfusion independence is a strong prognostic factor in unfit AML patients. Observations made in MDS (11) may now be extended to AML. In addition, AZA may improve quality of life by reducing requirements for transfusions and anemia symptoms. Prospective randomized trials are required to validate these observations in larger cohorts.

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SB, OS and MAD contributed to study design, data interpretation, and writing.

The authors report no conflict of interest. This work was not funded by external sources.

The retrospective data collection was approved by our university ethics committee for clinical research.

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Table 1. Baseline characteristics of study groups according to RBC transfusion independence.

		Total	Baseline or acquired RBC-TI	Never reached RBC-TI	P**
N		38	22	16	
Age	Years	68 [25-86]	72 [62-83]	66 [39-80]	0.04
	≥70	21 (55%)	14 (67%)	7 (41%)	NS
Gender	Female	24 (63%)	14 (67%)	10 (59%)	NS
Lab values at baseline					
Hb	g/l	85 [72-125]	87 [73-125]	82 [72-108]	NS
PLT	G/l	38 [7-517]	40 [7-128]	37 [14-517]	NS
WBC	G/l	3.1 [0.6-36.6]	3.9 [1.4-21.4]	2.9 [0.6-36.6]	NS
ANC	G/l	0.5 [0.0-6.0]	0.6 [0.0-3.1]	0.3 [0.1-6.0]	NS
PB blasts	%	14 [0-91]	10 [0-91]	39 [0-90]	NS
BM blasts	%	70 [20-90]	73 [20-90]	70 [20-90]	NS
	≥30%	29 (83%)	15 (80%)	14 (87%)	NS
	≥50%	21 (60%)	11 (55%)	10 (67%)	NS
RBC units over 8 weeks prior to AZA start		2 [0-16]	1 [0-16]	2 [0-16]	NS
Cytogenetic risk group*	Favorable	3 (8%)	2 (10%)	1 (6%)	
	Intermediate	21 (64%)	12 (57%)	11 (65%)	NS
	Adverse	11 (29%)	7 (33%)	4 (24%)	
Diagnosis	Primary AML	16 (42%)	8 (28%)	8 (62%)	
	Transformed MDS	17 (45%)	14 (63%)	3 (19%)	NS
	Refractory/relapsed	5 (13%)	2 (9%)	3 (19%)	
Time from diagnosis to AZA	Months	0.4 [0.0-12.9]	0.3 [0.1-12.6]	0.6 [0.0-13.0]	NS

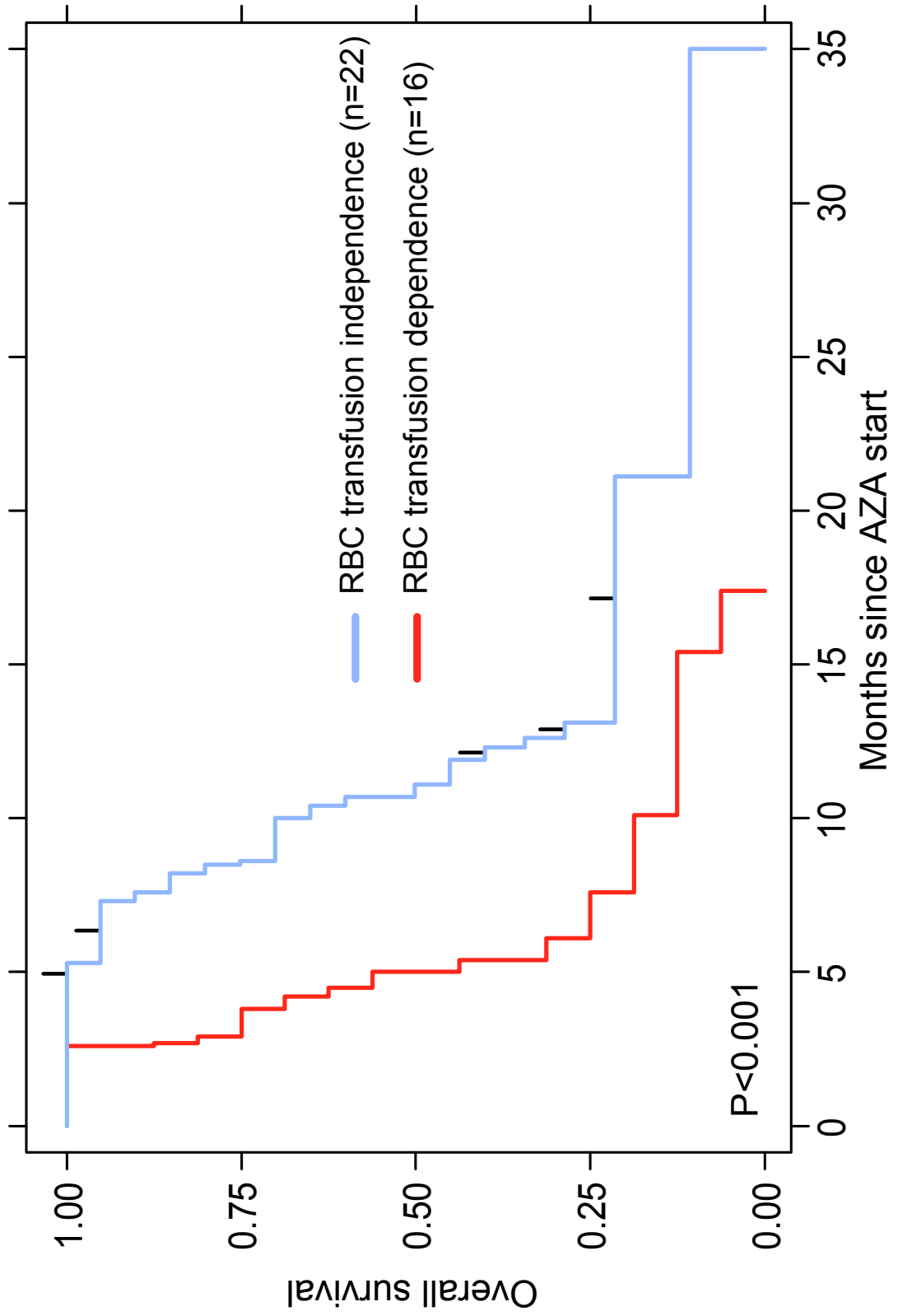
For continuous data median is shown, [] range. RBC-TI, red blood cell transfusion independence. *Definition of cytogenetic groups was according to HOVON classification (12), NA for 1 patient in never TI group. ** Mann-Whitney test, NS: P>0.05.

Figure legend

Figure 1. Survival according to RBC-transfusion independency.

A. Overall survival of patients according to transfusion needs. We analyzed 38 patients : 22 RBC-transfusion independent (blue) and 16 RBC-transfusion dependent (red). OS 11.1 vs 5.0 months, $P=0.0006$. Twelve-month survival rate were 40% [95CI 19-60%] and 13% [95CI 2-32%] respectively. **B.** Overall survival of patients with transfusion independence (TI) according to baseline transfusion needs ($n=22$). Median OS was 10.7 months for baseline TI ($n=6$, blue) vs. 11.9 months for TI acquired under AZA ($n=16$, red), 12-month OS 40 [95CI 17-63%] vs. 45% [95CI 5-75%], $P=NS$.

A



B

