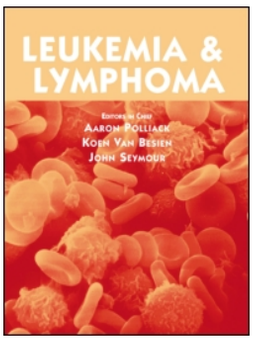

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Pre-treatment with oral hydroxyurea prior to intensive chemotherapy improves early survival of patients with high hyperleukocytosis in acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia with high white blood cell count (WBC) is a medical emergency. A reduction of tumor burden with hydroxyurea may prevent life-threatening complications induced by straight chemotherapy. To evaluate this strategy, we reviewed medical charts of adult patients admitted to our institution from 1997 to 2011 with non-promyelocytic AML and WBC over 50 G/L. One hundred and sixty patients were included with a median WBC of 120 G/L (range 50–450), 107 patients received hydroxyurea prior to chemotherapy, and 53 received emergency induction chemotherapy (CT). Hospital mortality was lower for patients treated with hydroxyurea (34% versus 19%, $p = 0.047$) even after adjusting for age ($p < 0.01$) and initial WBC count ($p = 0.02$). No evidence of any difference between treatment groups in terms of WBC decline kinetics and disease free survival ($p = 0.87$) was found. Oral hydroxyurea prior to chemotherapy seems a safe and efficient strategy to reduce early death of hyperleukocytic AML patients.

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Introduction

High hyperleukocytosis (white blood cell (WBC) count from 50 to 100 G/L) is observed in 15–20% of all newly diagnosed acute myeloid leukemia (AML) patients.[1–3] In this population, an excessive rate of initial life-threatening complications that can also worsen rapidly after the initiation of intensive chemotherapy is commonly reported.[4] Despite the lack of consensus on early death definition and WBC count threshold, approximately 20–25% of these patients die before achieving a complete remission.[3,5,6] Indeed, leukostasis due to sludging blast cells in capillary bed is observed in 35% of these patients and responsible for cerebral and/or respiratory failure.[7] In addition, tumor lysis syndrome, related to high tumor burden and proliferation, can lead to cardiac failure or acute kidney injury.[8] Finally, disseminated intravascular coagulation (DIC) contributes to life threatening bleeding.[9] All these conditions may preclude the possibility of inclusion in prospective trials,[10] and, therefore, limit our knowledge about this specific population.

To date, several strategies have thus been tried in order to reduce the mortality triggered by fast institution of intensive chemotherapy in these patients. Emergency leukapheresis is commonly offered but there is conflicting data regarding its benefits.[2,11,12] In specific subgroups of patients, a high rate of complication of this procedure has also been reported.[13] Early admission to the intensive care unit (ICU) for aggressive monitoring and administration of systemic high-dose steroid to reduce leukostasis associated endothelial damage have also been proposed with encouraging results.[14,15]

Finally, administration of oral hydroxyurea (HU), an anti-proliferative drug that interfere with DNA synthesis and adhesion molecule expression of endothelial cells,[16,17] to gradually lower the WBC count prior the intensive chemotherapy, became common practice in several centers. This strategy has long been recognized in improving leukostasis-related complications in very small

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series [18,19] and more recently was recommended by international guidelines.[20] Nevertheless, this approach has never been formally evaluated. In this study, we aimed to retrospectively assess the toxicity and benefit of the administration of HU prior to intensive chemotherapy in comparison to the emergency chemotherapy strategy for patients with hyperleucocytic AML.

Materials and methods

Patients

All consecutive adults (> 15 years old) patients admitted in our institution between 1997 and 2011 with a newly diagnosis of AML according to OMS classification were retrospectively included if they had an initial WBC count exceeding 50 G/L. Acute promyelocytic leukemia (FAB M3), AML relapse and patients unfit to receive intensive chemotherapy because of advanced age or severe comorbidities, were not included. Datasets were anonymously extracted from medical charts and laboratory records.

Treatments and procedures

During the study period, two different strategies have been used alternatively in our institution to manage hyperleukocytic (WBC count over 50 G/L) AML, according to the clinician in charge of the patient. In the first strategy, patients received straight emergency induction chemotherapy (CT) based on a combination of anthracycline and cytarabine (Supplementary Table 1) started during the first 24 h after admission in hospital, regardless of their WBC count. In the second strategy, patients were given emergency HU 50–75 mg/kg/d orally or via a gastric tube as recommended.[20] In these patients, HU was interrupted and induction chemotherapy started when WBC count had decreased below 20G/L or earlier in case of slow blast clearance. All patients had a close monitoring (at least three times a day) of clinical and biological parameters and a fast institution of life sustaining therapy in case this was required. Induction chemotherapy regimens are described in Supplementary Table 1 and were the same in both groups.

Supportive care and prevention of TLS were managed according to recommendations.[21] DIC management did not change over the study period and was based on the local guidelines that were subsequently published by international expert panel.[22] Platelets and fresh frozen plasma (15–30 mL/kg) transfusions were infused to maintain platelets over 50 G/L prothrombin time below 1.5N and fibrinogen over 1.5 g/L. Heparin was not used, except in case of thrombotic complications.

In a subset of patients with respiratory signs and FAB M4/M5 AML, dexamethasone was added to chemotherapy after 2005.[15] Patients who did not reach complete remission (CR) after the first course of chemotherapy received a salvage regimen if they had no uncontrolled infection or poor performance status. After CR, consolidation chemotherapy or allogeneic hematopoietic stem cell transplantation was done, according to age, comorbidities, oncogenetic classification, and donor availability.

Statistical analysis

Descriptive statistics, that is, percentage for qualitative variables and median with interquartile range (IQR) for continuous variables, are reported. Point estimates are given together with 95% confidence intervals (CI). Patients' characteristics and safety outcomes were compared with the exact Fischer test for categorical variables and Wilcoxon rank sum test for continuous variables. The origin date used to measure all the outcomes was the latest between the day of first hospital admission and the day of AML diagnosis. Cumulative incidence of hospital mortality was estimated in a competing risks framework, and compared across treatment groups using Gray's test.

Then, to handle potential confounding, we first adjusted the outcome comparison across treatment groups using a multivariate logistic regression model, including variables selected to hospital mortality by univariate analyses. To avoid missing data in covariates, a procedure of multiple imputation by chained equations (R package MICE) was used for the multivariate analysis, so that results are averaged on the 30 complete imputed datasets.

Second, to balance the distribution of baseline covariates between the patients treated with HU and those receiving straight chemotherapy (CT), we computed a propensity score (PS). This was based on a multivariate logistic model estimating the probability for each patient to have received HU given his (her) initial characteristics. The model included all potentially prognostic information. This was done in each of the 30 imputed datasets (as described above), and the average score was used as the PS value. Then, each patient in the HU group was matched with no replacement with a CT group patient on their PS, on the basis of a nearest neighbor search, using calipers of 0.2 SD of the logit PS. Matched datasets were finally used to assess the benefit of HU in terms of hospital mortality using mixed effect models to handle matching.

All tests were two-sided and a p value of 0.05 was considered as statistically significant. Statistical analysis

Table 1. Patients characteristics according to the group of treatment.

		HU group	CT group	*p*
Patients	*n*	107	53	
Age (years)	Median [IQR]	44[31; 60]	50[34;64]	0.39
Sex (male)		57(53%)	27(51%)	0.87
≥1 comorbidity		35(33%)	18(34%)	0.86
Year of diagnosis	1997–2002	21(20%)	34(64%)	<0.001
	2003–2008	52(48%)	17(32%)	
	2009–2011	34 (32%)	2(4%)	
Initial management				
Time from first symptom to diagnosis (days)	Median [IQR]	17[9; 32]	17.5[7; 30]	0.53
Time from first blood count to admission (days)	Median [IQR]	1[0; 2]	0[0;1.25]	0.26
Transfer from another hospital		61(57%)	31(58%)	1.00
Clinical parameters				
Performance status (ECOG)	0–1	78(73%)	31(58%)	0.17
	2	21(20%)	14(26%)	
	≥3	8(7%)	7(13%)	
	NA	0(0%)	2 (4%)	
≥1 extramedullary localisation		70 (65%)	37 (70%)	1
Leukostasis	Respiratory	43 (40%)	24 (43%)	0.61
	neurologic	14 (13%)	5 (9%)	0.61
DIC		19 (18%)	13 (25%)	0.4
TLS		58 (54%)	36 (68%)	0.086
Biological presentation				
WBC (G/L)	Median [IQR]	124 [83; 196]	120 [82; 200]	0.7
Hb (gr/L)		90 [80; 110]	93 [80; 115]	0.38
Platelet count (G/L)		58 [30; 90]	54 [26; 84]	
LDH (xULN)		3.1 [2; 4.9]	2.6 [1.6; 5.4]	0.26
Creatinine (μmol/L)		93 [71; 118]	97 [79; 131]	0.42
Disease characteristics				
FAB classification	M0	3(3%)	0(0%)	0.22
	M1	23(21%)	8(15%)	
	M2	15(14%)	5(9%)	
	M4	21(20%)	11(21%)	
	M4Eo	14(13%)	6(11%)	
	M5	27(25%)	17(32%)	
	Multilineage dysplasia	4(4%)	2(4%)	
	not classified	0(0%)	4(8%)	
De novo AML		94(88%)	48(90%)	0.8
Secondary AML	Therapy-induced	11(10%)	2(4%)	0.14
	post MPD or MDS	2(2%)	3(6%)	0.26
Karyotype (MRC)	Favorable	16(15%)	8(15%)	0.38
	Intermediate	69(64%)	30(57%)	
	Adverse	15(14%)	12(22%)	
	Failure	2(2%)	1(2%)	
	not done	5(5%)	2(4%)	
FLT3 ITD mutation		34/95(36%)	10/29(34%)	1
FLT3 TKD mutation		10/89(11%)	6/20(30%)	0.073
NPM1 mutation		26/68(38%)	7/12(58%)	0.22
Associated management				
Prospective trial inclusion		32(30%)	10(19%)	0.04
Early ICU admission		23 (21%)	13(19%)	1.00
Dexamethasone administration		32(30%)	11(21%)	0.44

DIC, disseminated intravascular coagulation; TLS, tumor lysis syndrome; WBC, white blood cell; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal; FAB, French American British; AML, acute myeloid leukemia; MPD, myeloproliferative disease; MDS, myelodysplastic syndrome; MRC, Medical Research Council; FLT3, Fms-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain; NPM1, nucleophosmine; ICU: Intensive care unit.

was performed using the R 2.13.0 software (http://www.R-project.org/).

Results

Patient baseline characteristics

Among the 1336 adult patients admitted in our institution from 1997 to 2011 with a newly diagnosed AML, 260 had a WBC over 50 G/L (Figure 1). After exclusion of promyelocytic AML, relapsed AML and patients unfit for intensive chemotherapy, 160 patients were evaluable with sufficient outcomes data. These patients could be separated into two groups: 107 patients received oral HU prior intensive chemotherapy (HU group) and 53 patients received straight emergency chemotherapy (CT group). Overall, the median follow-up time of censored subjects was 3.1 years.

In the HU group, the median dose of HU received was 50 [IQR 39–61] mg/kg/d during a median time of 4 [IQR 2–6] d. In the CT group, the chemotherapy was administered the same day [IQR 0–1] of hospital admission in median. Among them, 35 patients (65%) received

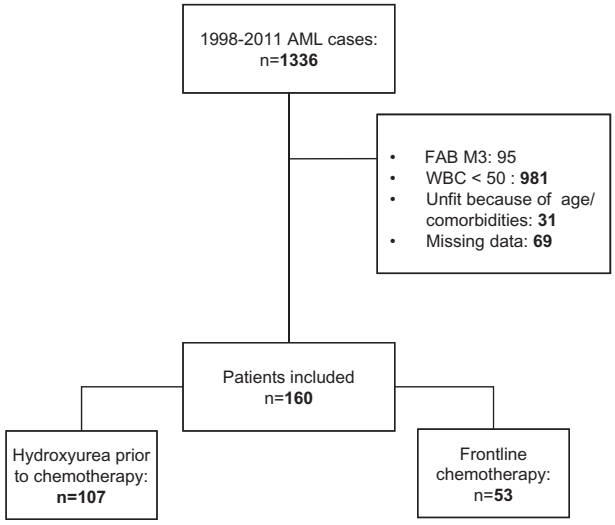

Figure 1. Flow chart of patients study inclusion.

a halved dose of anthracycline alone in the first day. The remaining patients received a full dose of anthracycline plus cytarabine on the same day and no patient received cytarabine alone first because of the potential lung toxicity of this drug.

Baseline clinical and biological characteristics of the patients according to treatment groups are shown in Table 1. Median initial WBC count was 120 G/L (range 51–354). A high proportion of complications were observed in both groups: 43% had clinical signs of leukostasis, within the first 2 d of AML diagnosis which were manifested by respiratory signs in 42%, or neurological signs in 12%. DIC and tumor lysis syndrome (TLS) were found in 20% and 59% of the patients, respectively, with no difference ($p = 0.4$ and $p = 0.08$). Most of the patients included in this study had spontaneous TLS before any treatment. However, we observed trend toward more, cases of biological TLS during the first 48 h in non-HU group as compared to HU group (68% versus 54% $p = 0.086$). Renal replacement therapy requirement was equally distributed (28 in HU and 14 in CT, 52% versus 44%, $p = 0.5$). About these 28 patients in the HU group, the median time between HU and renal replacement therapy was 2 d, the baseline median creatinine serum level was 121 μmol/L (71–676) and finally 20/28 had clinical TLS criteria before starting HU.

Karyotype analysis was available for 150 patients (94%) with no difference between groups. Half of the cases had a normal karyotype. Other cytogenetic findings were inv(16) in 15%, 11q23 rearrangement: 10%, complex karyotype (≥3 abnormalities): 5%, +8: 4.5%, t(6;9): 2.5%, −7/−7q: 2.5%, t(9;22), 9q−, inv(3), t(8;21), and iso(17q) accounted for the remaining cases (<2% each). Molecular analysis of *FLT3* and *NPM1* genes were available for 92 patients overall. *FLT3* Internal Tandem Duplication (*FLT3*-ITD) was found in 35%, *FLT3* TKD mutation in 15%, and *NPM1* mutation in 41% of the patients. $NPM1m^+/FLT3\text{-}ITD^-$ accounted for 37% of the normal karyotype patients and no difference in leukemiaNet classification subgroups repartition between the two groups was retrieved ($p = 0.34$). Finally, no difference was observed between each treatment group according to clinical presentation, transfer from another medical center, WBC count, FAB classification, cytogenetic group, and molecular abnormalities repartition. However, HU strategy was increasingly used over the time ($p < 0.001$) as illustrated in Table 1.

A short course of dexamethasone (10 mg every 6 h until neutropenia) was administered in a subset of 43 FAB M4/M5 patients with respiratory failure with no statistical difference between the two groups (30% versus 22%, $p = 0.44$). Because Dexamethasone was prescribed for more severe patients, we could not evaluate the effects of the combination with HU. Thirty-six patients were admitted in the ICU for monitoring purpose with no difference between the two groups ($p = 1.0$). In addition, there was no difference in early ICU admission (direct ICU admission) between both groups (70% versus 74%, $p = 0.62$).

Forty-two patients were included in a prospective trial (ALFA-9801: 2, ALFA-9802: 24, ALFA-9803: 1, CBF-2006: 4, ALFA-0701: 3, ALFA-0702: 8). Thirty-two were in the HU group (30%) and 10 in the CT group (18%) ($p = 0.04$). Included patients had a median age of 36 years old and a median WBC count of 95 G/L [IQR: 69–136].

Effect of hydroxyurea on in-hospital mortality

In the HU group, five patients died before the start of intensive chemotherapy, two of whom received only one dose of HU. In the CT group, six patients died before the end of scheduled induction regimen chemotherapy. Nevertheless, all patients were kept in their primary group for the analysis in an effort to reduce the attrition bias.

In-hospital death occurred for 18 patients in the CT group and 20 in the HU group (34% versus 19%, $p = 0.047$) as shown in Supplementary Figure 2. Identified causes of in hospital death were infection for 11 patients (29%), pulmonary leukostasis for nine patients (24%) and cerebral bleeding or thrombosis for seven patients (18%).

Univariate logistic regression analysis of factors potentially affecting outcomes identified that preexisting conditions, tumor burden surrogates, signs of inaugural complications, and the CT group of treatment were significantly associated with hospital mortality (Table 2). However, there was no evidence of any

prognostic value of FAB M4/M5, secondary AML, and year of diagnosis.

Based on a multivariate analysis, belonging to the HU group was still associated with a decreased hospital mortality (OR: 0.29 [0.1–0.84] $p = 0.02$), adjusted on age (OR: 1.07 [1.03–1.11] $p < 0.01$), and initial WBC count (OR: 1.01 [1.0–1.1], $p = 0.02$), both considered as deleterious.

A propensity score was then used to match the outcome comparison of the treatment groups on potential confounders. Only 44 of the 107 (41%) HU patients could be matched to one of the 53 CT patient, resulting in a matched population of 88 patients. The hospital survival benefit of HU in this matched sample was slightly decreased (OR: 0.3 [0.08–1.09], $p = 0.067$).

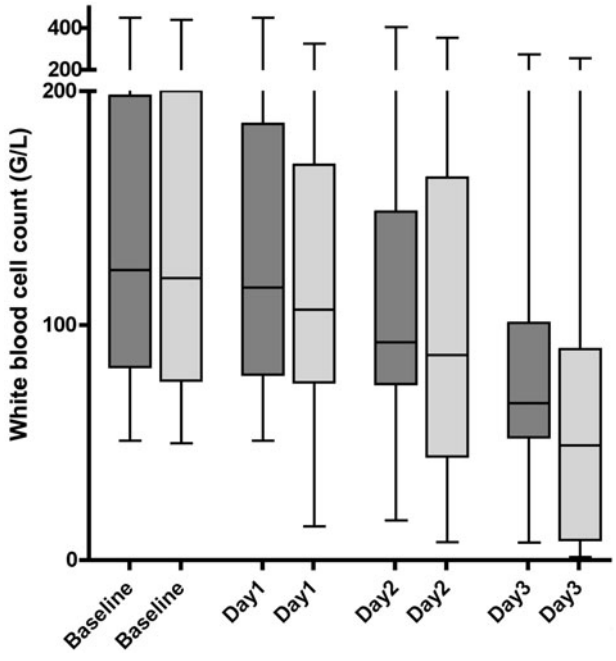

Figure 2. White blood cell count evolution according to treatment group (dark gray: HU (hydroxyurea) group, light gray: CT (chemotherapy) group.

Complete remission was achieved in 79 (73%) patients in the HU group and in 31 (55%) of the CT group after a salvage course of chemotherapy in 7.5% and 17%, respectively. About 85% of the patients included in a prospective trial ultimately reached CR. Finally, after complete remission (CR), the 1-year DFS was 59% in the CT group (CI 95%: 39–74%) and 54% (CI 95%: 41–65%) in the HU group ($p = 0.11$). Only four patients (two in each group) died while in first CR, all of them after bone marrow transplantation.

As detailed in Supplementary Table 2, the very early mortality before day 14 of hospital admission was associated with a greater time interval from diagnosis to admission and with the transfer from a primary care center in addition to the other parameters identified in the hospital mortality analysis. After multivariate analysis, only DIC was associated with very early mortality (OR 6.24, CI 1.15–33.7, $p = 0.03$).

Hydroxyurea safety analysis

We did not find an excess rate of adverse event in the HU treated patients. Bacterial (15% versus 19%, $p = 0.66$) and fungal (25% versus 32%, $p = 0.46$) infection rate were similar in both groups. Furthermore deep vein thrombosis or arterial thrombosis (10% versus 12%, $p = 0.79$) arose in both groups with the same frequency. Severe hemorrhagic complications occurred for seven patients in the HU group (two intra-alveolar hemorrhage (IAH), five intra-cerebral hemorrhage (ICH)) and for 10 patients in the CT group (four IAH, five ICH, and one

Table 2. Univariate and multivariate predictive analyses of hospital mortality.

	Univariate analysis			Multivariate analysis		
	OR	95 CI	*p* value	OR	95 CI	*p* value
HU group of treatment	0.45	0.21–0.94	0.03	0.29	0.1–0.84	0.02
Age (continuous variable)	1.1	1.03–1.08	<0.01	1.1	1.03–1.11	0.00
Comorbidity	2.2	1.06–4.73	0.03	0.9	0.26–2.86	0.81
Performance status (ECOG)	2	1.28–3.17	0.02	1.0	0.53–2.01	0.92
Baseline WBC (continuous variable)	1	1–1.01	<0.01	1.0	1–1.01	0.02
Disseminated intravascular coagulation	4	1.76–9.22	<0.01	2.8	0.82–9.89	0.1
Baseline LDH	1.2	1.01–1.34	0.042	1.1	0.9–1.34	0.31
Clinical leukostasis	4.4	2.04–9.57	<0.01	0.4	0.07–2.48	0.33
Abnormal respiratory exam	5	2.27–11.16	<0.01	2.0	0.35–11.86	0.42
Abnormal neurological exam	3.5	1.29–9.34	0,01	2.0	0.51–8.12	0.31
Tumor lysis syndrome	3.3	1.42–7.87	<0.01	0.6	0.15–2.49	0.49
Baseline platelet count	1	0.99–1	0.19	–	–	–
Baseline creatinine	1	1–1.01	0.24	–	–	–
Time from diagnosis to admission (days)	1.4	0.86–2.45	0.15	–	–	–
Transfer from another center	1.9	0.87–4.25	0.10	–	–	–
FAB M4/M5	0.7	0.34–1.6	0.44	–	–	–
Secondary AML	1.4	0.43–5.1	0.53	–	–	–
Year of diagnosis	0.9	0.84–1	0.06	–	–	–

OR, odds ratio; 95 CI, ninety-five percent confidence interval; AML, acute myeloid leukemia.

digestive bleeding) and was responsible for two and eight deaths, respectively. Fifty percent of the HU group and 60% of the CT group patients were admitted in the ICU ($p = 0.24$). We did not find any difference in life support requirement between the two groups. Half of the ICU patients required invasive mechanical ventilation (54% HU versus 53% CT, $p = 1.00$) for either neurologic or respiratory failure. Renal replacement therapy was used for 28 HU and 14 CT patients (52% versus 44%, $p = 0.5$).

Figure 2 shows the WBC decline according to both groups. In HU group patients that received HU, median WBC count at the time of chemotherapy initiation was 39 [13–87] G/L corresponding to a 67 [88–22] % decrease compared with the baseline. This drop reached 83 [94–58] % in the subset of patients that received at least 48 h of HU. Only four patients experienced WBC rise (+10%) during HU treatment. All four patients received HU at less than 50 mg/kg/d for less than 2 d. A correlation between HU dosing and WBC decline is shown in Supplementary Figure 3.

Discussion

Because of the absence of any randomized trial and the fact that clinical choices are crucial within the first hours, high hyperleukocytosis AML management still remains a medical challenge in 2015.[23] Indeed, a high level of decision heterogeneity is observed among clinicians who have to deal with these patients. In this study, we systematically analyzed a large cohort of hyperleukocytic AML patients that received HU or straight emergency intensive chemotherapy. After adjustment on short-term prognostic parameters, toxicity and efficacy data advocate the use of oral HU before chemotherapy for this specific population.

On one hand, this drug has been used to reduce leukostasis induced pulmonary and cerebral harm a long time ago in very small series of hyperleukocytic AML.[18,19] In Grund et al. study, patients receiving high-dose HU at the time of leukemia diagnosis did not experience the life-threatening complication commonly reported in this situation. In our study, hospital mortality concerned 23% of the cohort (14% before day 14) and is similar to the more recently reported rates.[3–5,11]

On the other hand, leukapheresis has been preferred in many centers because of the fast ability in clearing blast cells from the peripheral blood.[2,23,24] However, other authors subsequently provided data that questioned the usefulness of this procedure regarding early mortality prevention.[11,12,25] In addition, leukapheresis was suspected to be associated with specific complications, and often with the requirement for central venous access which could be hazardous in patients with hemorrhagic diathesis related to a diffuse intravascular coagulation.[13] A recent meta-analysis concerning those management approaches failed to identify a preferred strategy,[5] but the studies used for this analysis mainly enrolled patients who received a mix of different strategies at different times, and dosage of HU were not provided. Finally, delaying intensive chemotherapy appeared to be puzzling to others [26] and despite a recent analysis about the safety of not providing emergency chemotherapy,[27] some clinicians believed that intensive chemotherapy should be provided as soon as the AML diagnosis is made.

At present, we lack strong evidence regarding the impact of delaying chemotherapy because of numerous obstacles for including these patients in prospective trials. First, they frequently have baseline exclusion criteria defined by cooperative group protocols (low performance status, renal failure, etc.). Second, they may not be able to provide their consent because of life-threatening conditions. Finally, inclusion may not be considered because of the feeling that the situation requires immediate intervention. We show here that HU may provide time and clinical improvement that will allow clinicians and patients to safely achieve better conditions for inclusion in a prospective trial (30% versus 19% of prospective trial inclusion in our study, $p = 0.04$).

In hyperleukocytic AML patients, starting chemotherapy can be worrisome, and small retrospective series proved that an excessive rate of cardiac or lung complications, as high as 50%, occurs in the first hours after the start of chemotherapy.[28–30] Indeed, clinical TLS intensity is exacerbated and seems proportionate to the baseline tumor load level and WBC count. Also, *in vitro* data provided evidence that chemotherapy induces a reduction of blast cell membrane deformability that could account for observed respiratory deterioration.[31] Lastly, DIC and associated dramatic bleeding are commonly exacerbated by intensive chemotherapy because of the release in circulation of pro-coagulant factors by the bulk of blast cells. In all AML prospective trials, baseline WBC count is strongly associated with hospital mortality.[32] In our real-life study, we also observed a high rate of baseline AML-related complications (tumor lysis syndrome 58%, leukostasis 42%, and DIC 20%) that is consistent with an appropriate selection of patients requiring urgent management.

We were also able to retrieve cytogenetic and molecular data for the majority of patients included in this study. As presumed, we confirmed a high rate of FLT3 internal tandem duplication (35%) that could partially account for the dismal long-term outcome of these patients.[33]

This study has several limits. The main concern is related to the fact that the constitution of both groups was not based on the randomized experiments but rather on clinician decision. During the study period, a local procedure guideline for the management of such patients was not formally written. Despite a gradual decline in the use of straight chemotherapy, two patients did not received HU in the most recent period due to clinicians in charge habits. Apart from the study period, we were thus not able to assess other factors that have interfered with this decision. In the aim to minimize potential selection bias, we used a propensity score to compare the groups and avoid interference of other prognostic parameters. However, this resulted in a sample size decrease of 88 (55%) of the original set of 160 patients, likely responsible for some lack of statistical power when testing the effect of the treatment. Second, because of the rarity of hyperleucocytic patients, we decided to include patients among a 14 years period of time during which supportive care and early mortality improved in general AML population.[34–38] Nevertheless we could not find an independent prognostic impact of the inclusion date. Third, the high rate of early death in this study precludes an accurate analysis of the long-term outcomes because of this lack of power. Finally, we are not addressing the biological mechanism of HU efficiency and further biological studies may thus be required. It is not known if HU acts via a smooth tumor debulking or rather interfere with the endothelium-blast cell adhesion as it has been previously shown to act on neutrophils cells in sickle cell disease.[17]

This study is the first systematic report of HU efficiency and toxicity in a hyperleucocytic AML cohort. It suggests that a strategy based on the emergency administration of oral HU is safe, may reduce the rate of early death, and provide enough time to include patients in prospective trials.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.3109/10428194.2016.1142083.

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