The use of hydroxyurea pretreatment in chronic myeloid leukemia in the current tyrosine kinase inhibitor era

The added value of hydroxyurea (hydrea) as a treatment modality in chronic myeloid leukemia (CML) is limited since the availability of tyrosine kinase inhibitors (TKI). Nonetheless, many clinicians still use it as a temporary treatment while awaiting a definite diagnosis to achieve some cytoreduction and alleviate symptoms due to hyperleukocytosis.[1] However, it is uncertain if early cytoreduction with hydrea confers any benefit for patients, particularly in the absence of symptomatic hyperleukocytosis. Several reports even hinted that hydrea had an antagonistic effect on subsequent imatinib responses, but this was only observed with extended use of hydrea (>6 months,[2] >12 months[3]).

Current European LeukemiaNet (ELN) recommendations advise that a short course of hydrea may be given in symptomatic patients with high leukocyte or platelet counts while molecular and cytogenetic confirmation of the CML diagnosis is pending.[4] However, the impact of hydrea pretreatment has not been specifically studied so far and it remains unclear how this recommendation is applied in real-world clinical practice. The objectives of this study were to evaluate the use of hydrea as a pretreatment modality in a population-based nationwide CML-cohort treated in the TKI era, to assess its influence on achieving the ELN response milestones and the occurrence of hematotoxicity during subsequent TKI therapy.

We performed a retrospective analysis on data from a real-world population-based Dutch patient cohort from the PHAROS CML Registry (445 patients diagnosed between 2008 and 2014) and HemoBase (35 patients diagnosed between 1999 and 2015). Additional information on both registries can be found in Geelen *et al*.[5] Patients were included if diagnosed in chronic phase (CP) according to the ELN criteria, treated with a TKI in first line and if sufficient treatment information was available. Patients were grouped based on having received pretreatment with hydrea. Hematologic, cytogenetic, molecular responses and response milestones were defined as described in the ELN recommendations.[4] In the registry, *BCR-ABL1* levels were reported as a percentage on the International Scale (%IS) or as a log reduction of *BCR-ABL1* transcripts from baseline in case molecular laboratories were unable to report on the IS at that time. The achievement of ELN response milestones was assessed at 3, 6 or 12 months with a margin of 1 month for each point in time. Differences between proportions were tested using the Chi-square method with a Bonferroni correction for multiple testing. For the time-to-response analysis, the Fine & Gray cumulative incidence competing risk (CICR) method was used with the start of TKI treatment as time point zero and death or progression to acceleration phase or blast crisis as a competing event. The achievement of a complete cytogenetic response and/or a BCR-ABL1-value <1%IS or a two log reduction (CCyR/MR2.0) were pooled in the time-to-response analysis since they represent an equivalent disease burden.[6] However, in the main CICR analysis, patients without standardized (IS) molecular results were excluded. A Fine & Gray competing risks (CR) regression model was used for multivariable analysis including sex, age, EUTOS long term survival score (ELTS), leukocyte count at diagnosis and first-line TKI generation as covariates. Missing values in covariates were handled using substantive model compatible fully conditional specification (SMC-FCS) multiple imputation. A second CICR analysis for responses was performed on propensity score matched cohorts. A *P*-value lower than 0.05 was considered significant. All statistical analyses were performed in SPSS (version 24) and R (version 1.3.1093). The Medical Ethics Committee of the Erasmus Medical Center in Rotterdam approved this study and the exemption from informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The PHAROS CML Registry combined with HemoBase comprises a total of 480 CML patients. Four patients underwent leukapheresis for hyperleukocytosis, 15 patients were diagnosed in advanced phase disease according to the ELN criteria, for 54 patients we had insufficient treatment information available and five patients were not treated with a TKI in first line. These patients were excluded from further analyses.

Out of 402 included patients, 175 (44%) patients received hydrea pretreatment. Hydrea pretreatment was given more frequently in the first decade after the introduction of imatinib (2003-2010) than after 2010 (2011-2015; 48% *vs*. 35%, *P*=0,012). Hydrea-treated patients had a less favorable risk profile based on Sokal score or ELTS, and more often reported constitutional symptoms (36% *vs*. 25%, *P*=0.027) or symptomatic splenomegaly (25% *vs*. 12%, *P*=0.001) at diagnosis (Table 1). Median leukocyte count was higher in hydrea-pretreated patients (Figure 1A), of whom 21% had a relatively low leukocyte count below $100x10^9$/L. Symptomatic hyperleukocytosis with clinical signs of hyperviscosity was more prevalent in hydrea-pretreated patients, but constituted a minority of patients (10% *vs*. 3%, *P*=0.005). Also, approximately 40% of hydrea-treated patients were asymptomatic.

Table 1. Baseline characteristics, treatment characteristics and adverse events in patients with or without hydrea pretreatment.

	No hydrea (N=227)		Hydrea pretreatment (N=175)		*P*-value
Baseline characteristics	**N**	**%**	**N**	**%**	
Sex, male	116	51	108	62	0.034
Age at diagnosis (years), mean (SD)	57.5 (16,8)		54.0 (16.6)		0.039
Sokal score, low/intermediate/high	59/102/45	29/50/22	31/65/61	20/41/39	0.002
ELTS, low/intermediate/high	111/72/23	54/35/11	60/64/33	38/41/21	0.004
Leukocytes, x10^9/L median (IQR)	70.6 (37.6-142.1)		195.0 (118.0-283.4)		<0.001
Hyperleukocytosis*	84	37	136	79	<0.001
Symptomatic hyperleukocytosis	6	3	17	10	0.005
Symptoms, any	89	43	98	60	0.001
Constitutional symptoms	51	25	55	36	0.027
Symptomatic splenomegaly	26	12	43	25	0.001
Treatment characteristics					
Time from diagnosis to start first line TKI (days), median (IQR)	11.0 (1.0-21.0)		17.0 (7.0-29.0)		0.001
Hydrea treatment duration (days), median (IQR)	-		14.0 (8.0-26.5)		-
First line TKI, imatinib/2GTKI	178/49	78/22	135/40	77/23	0.885
Adverse events					
Hematotoxicity on first line TKI, N (%)	24	11	43	25	<0.001
TKI reduction/interruption first line overall	77	34	72	41	0.167
TKI reduction/interruption first line due to hematotoxicity	19	8	29	17	0.018

SD: standard deviation; ELTS: EUTOS long term survival score; IQR: interquartile range; TKI: tyrosine kinase inhibitor; 2GTKI: second generation TKI. *Hyperleukocytosis was defined as a leukocyte count of >100x10^9/L.

The hydrea-treated group had a significantly longer interval between diagnosis and the start of first-line TKI treatment (21 *vs*. 15 days, *P*=0.002). After the start of TKI therapy, hematotoxicity occurred more frequently in hydrea-pretreated patients (25% *vs*. 11%, *P*<0.001) resulting in more hematotoxicity-related TKI dose reduction or interruption (14% *vs*. 8%, *P*=0.018).

No apparent benefit was observed for hydrea pretreatment for patients achieving a complete hematologic response (CHR), a partial cytogenetic response (PCyR) or a *BCR-ABL1* <10%IS by 3 months, a CCyR by 6 months or a MMR by 12 months (Figure 1B). Significantly less hydrea-pretreated patients achieved a *BCR-ABL1* <1%IS by 6 months (65% *vs*. 80%, *P*=0.015).

A total of 346 patients could be assessed for CCyR/MR2.0 and 304 patients for MMR. Molecular results were available as %IS (n=243) or as log-reduction (n=61). In these cohorts, 325 (94%) and 260 (86%) patients achieved CCyR/MR2.0 and MMR, respectively. For the following main CICR analysis, only patients with standardized molecular results (%IS) were included. The cumulative incidence of CCyR/MR2.0 by 6 months was 40% (95% confidence interval [CI]: 32-47) and 48% (95% CI: 41-56) for patients with or without hydrea pretreatment, respectively (Figure 1C). The cumulative incidence of MMR by 12 months was 44% (95% CI: 42-47) and 56% (95% CI: 47-64) for patients with or without hydrea pretreatment, respectively (Figure 1D).

Similar results were found in the propensity score matched cohorts with a cumulative incidence of CCyR/MR2.0 of 42% and 56% (*P*=0.056) by 6 months and a cumulative incidence of MMR of 43% and 52% (*P*=0.233) by 12 months for patients with or without hydrea pretreatment, respectively. Propensity scores were calculated with the following baseline parameters: age, sex, ELTS, leukocyte count, symptoms at diagnosis and time from diagnosis to start first-line TKI. The matched cohorts consisted of 262 and 242 patients for CCyR/MR2.0 and MMR, respectively.

In a univariable CR regression model, the subdistribution hazard ratio (SHR) of hydrea pretreatment for CCYR and/or *BCR-ABL1* <1%IS was 0.77 (95% CI: 0.62-0.96; *P*=0.022). The

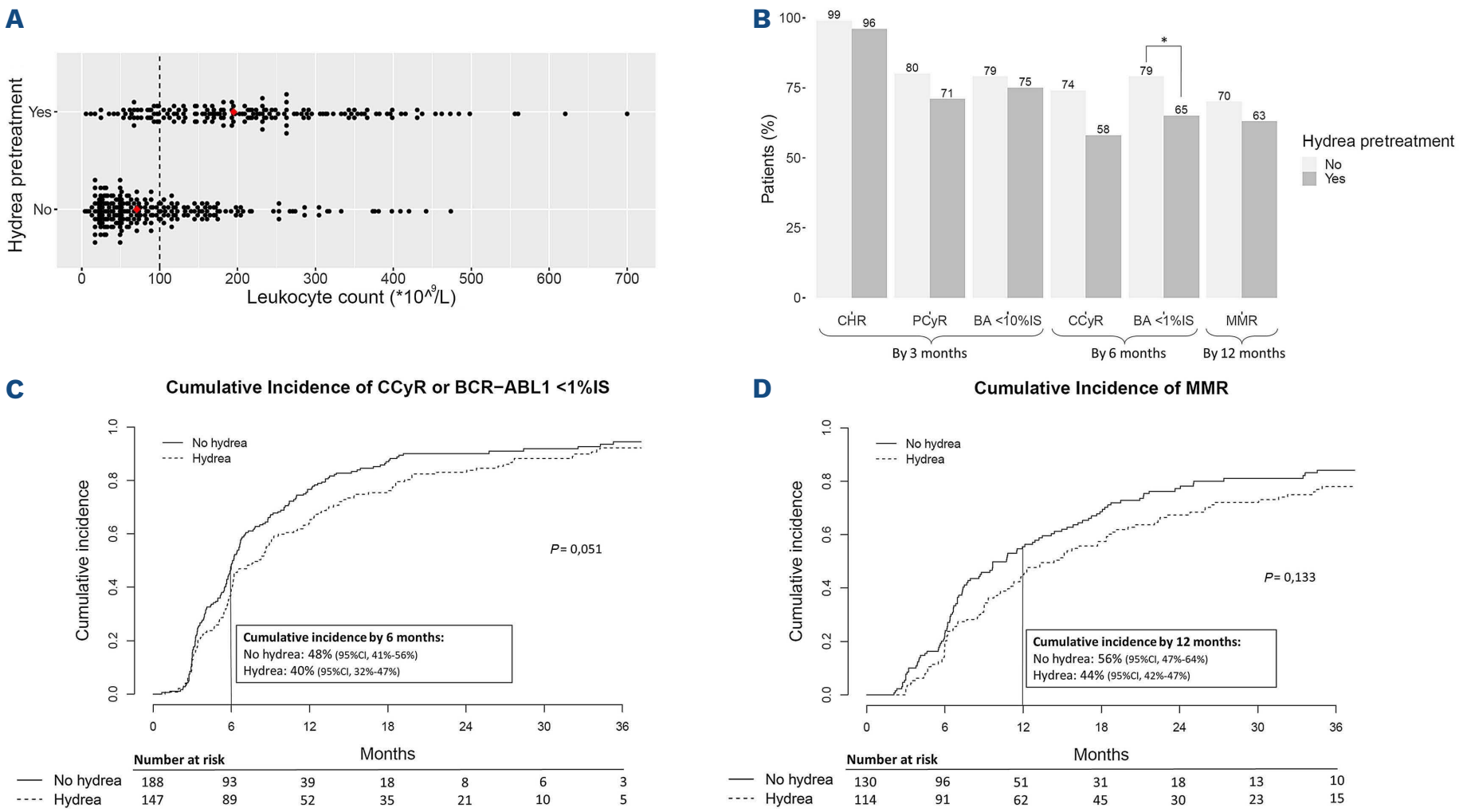

Figure 1. Characteristics of patients with *versus* without hydrea pretreatment. (A) leukocyte count (x10^9/L) at diagnosis. Red dots represent the median values in both groups; (B) proportion (%) achieving the ELN defined milestones by 3, 6 and 12 months; (C) cumulative of incidence of a complete cytogenetic response (CCyR) or BCR-ABL1 <1% on the International Scale (IS); (D) cumulative of incidence of a major molecular response (MMR). CHR: complete hematologic response; PcyR: partial cytogenetic response.

SHR of hydrea pretreatment in the multivariable model was 0.86 (95% CI: 0.67-1.12; *P*=0.274) for CCYR and/or *BCR-ABL1* <1%IS and 0.95 (95% CI: 0.72-1.26; *P*=0.722) for MMR. Of note, in both models ELTS and first-line 2GTKI remained strong, independent predictors for respective responses. In two subgroup multivariable analyses of patients with hyperleukocytosis (leukocyte count >100x10^9/L) and with first-line imatinib, the SHR of hydrea pretreatment for CCyR/MR2.0 were 1.04 (95% CI: 0.75-1.44; *P*=0.826) and 0.916 (95% CI: 0.69-1.21; *P*=0.535), respectively.

Hydrea pretreatment was used in nearly half of newly diagnosed CML patients in our cohort. Surprisingly, we observed a significantly longer delay in starting first-line TKI treatment in hydrea-pretreated patients. Furthermore, hydrea pretreatment was associated with a higher rate of hematotoxicity during first-line TKI treatment and hematotoxicity-related first-line TKI dose reduction or interruption. These patients had a longer median hydrea exposure (19 days) compared to patients without hematotoxicity (14 days), however this difference was not significant (*P*=0.251). Hematotoxicity did not occur significantly more in patients treated with a first-line 2GTKI.

Patients receiving hydrea pretreatment had no apparent benefit in achieving the ELN-defined responses both in the descriptive analysis by each milestone and in the time-to-response analysis, even while using the start of TKI therapy as time point zero. As expected, patients receiving hydrea pretreatment had a less favorable baseline profile with a higher ELTS and higher leukocyte count at diagnosis, but even after correction for these confounders hydrea pretreatment did not exert a beneficial effect on achieving treatment responses. In line with this, no differences in response rates were observed when assessing the subgroup of patients with hyperleukocytosis. Furthermore, response analysis in propensity score matched cohorts demonstrated a trend towards an antagonistic effect of hydrea pretreatment for the achievement of CCyR/MR2.0.

A limitation of this study is the retrospective character, assessing historical response data only until 2015. However, the time frame of our study corresponds with the implementation of first and second generation TKI in CML treatment recommendations and in clinical practice. Our population-based data indeed demonstrate a gradual decrease in the use of hydrea pretreatment. Still, even after 2010 at least 35% of patients were receiving hydrea pre-

treatment, including patients without a high leukemic load or symptom burden.

To our knowledge, this is the first study comparing clinical outcome in patients in relation to hydrea pretreatment in the TKI era. Our results indicate that early cytoreduction with hydrea has no added value in the treatment of CML for achieving the ELN response milestones and support current recommendation on restricting the use of hydrea pretreatment to patients with a symptomatic hyperleukocytosis or symptomatic splenomegaly while waiting for confirmatory diagnostic testing. Hydrea should not delay the start of TKI treatment as soon as the diagnosis is confirmed. More restrictive use of hydrea might shorten this delay and hematologists should be aware of the additional hematotoxicity of hydrea pretreatment on subsequent TKI therapy.

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Contributions

CK curated, analyzed and visualized the data, and wrote the first draft of the manuscript. PW conceptualized the research idea, provided supervision and wrote the final draft of the manuscript. IG provided an initial curation of the database and revised the manuscript together with the other co-authors. All authors revised and approved the final version of the manuscript.

Data-sharing statement

Data can be made available on request to other researchers, when in collaboration with the Dutch Cancer Registry, which is the owner of the data.

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