Macrocytosis and TKI Efficacy in Chronic Myeloid Leukemia

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Abstract

Introduction: Orally administered tyrosine kinase inhibitors (TKIs) are the cornerstone of treatment for patients with chronic phase chronic myeloid leukemia (CML). Currently, there is a paucity of validated predictive biomarkers to predict response to these medications. The identification and validation of a predictive biomarker of TKI response could conceivably aid clinicians in drug and dose selection. We aimed to evaluate treatment-emergent macrocytosis and clinical outcomes in CML patients taking TKIs.

Methods: This was a single-institution retrospective study that included patients (n=110) if they were $\geq$ 18 years old with chronic phase CML and who were treated with imatinib, dasatinib, nilotinib, bosutinib or ponatinib between January 1, 2010 to April 15, 2018. Patients were excluded if they lacked baseline and on-treatment mean corpuscular volume (MCV) measurements or baseline and on-treatment *BCR-ABL1* transcript measurements. The primary endpoint was incidence of complete hematologic response (CHR) at 30 days after TKI initiation. Secondary endpoints included time to CHR, early molecular response (EMR) and major molecular response (MMR) as well as EMR at 90 days and MMR at 365 days.

Results: The overall incidence of TKI-induced macrocytosis was low (n=7 or 6.4%) in the study population. Patients with treatment-emergent macrocytosis achieved CHR at median 26 days compared to 32 days in MCV $\leq$ 100 fL (HR=2.58, 95% CI [1.49-8.40]; *P*=0.009). A greater percentage of patients with MCV > 100 fL achieved CHR at 30 days, 87.5% vs 39% in patients with MCV $\leq$100 fL (OR=10.9, 95% CI [1.76-125.2] *P*=0.02). Significant associations between treatment-emergent macrocytosis and EMR or MMR were not observed.

Conclusions: Patients with treatment-emergent macrocytosis achieved CHR more rapidly compared to patients who did not. No difference was observed between treatment-emergent macrocytosis and EMR or MMR. Validation with a larger population of CML patients is needed to confirm the association between CHR at 30 days and MCV >100 fL based on the low incidence of macrocytosis in the study cohort.

Introduction

Chronic myeloid leukemia (CML) accounts for 15% of all leukemias.[1] In 2019, approximately 8,990 people were diagnosed with CML in the United States.[2] An approximate 1,140 deaths occur annually in patients in the United States with CML.[2] Oral tyrosine kinase inhibitors (TKI) have become the cornerstone treatment for chronic phase CML due to their ability to inhibit the activity of BCR-ABL, the oncoprotein which drives CML.[3,4] Although TKIs have dramatically changed the landscape of CML treatment, 6% of patients on TKIs still progress within 3 years.[5]

According to the European LeukemiaNet (ELN), the gold standard measurement of TKI response in CML is known as a major molecular response (MMR), which is defined $\leq$ 0.1% *BCR-ABL1* expression at 12 months of TKI therapy.[4] MMR is used routinely in clinic because it has been shown to be well-associated with overall survival (OS).[6,7] While clinical surrogate endpoints (e.g., MMR, complete hematologic response [CHR], and early molecular response [EMR]) are all used to monitor TKI response and efficacy in chronic phase CML, there is a paucity of validated predictive biomarkers that clinicians can use to determine which patients will benefit most from a particular TKI CML.[4] Identifying a predictive biomarker in CML could plausibly guide clinical decision making, and thus indicate when a patient may be over-treated and at risk for adverse events, or under-treated and at risk for therapy failure.

c-KIT is a receptor tyrosine kinase that is central to essential cellular processes, such as hematopoiesis and melanogenesis.[8] Mutations in *CKIT* can result in gene overexpression or altered c-KIT protein structure or function. These mutations, which are common in certain solid malignancies (e.g., gastrointestinal stromal tumor [GIST], commonly result in c-KIT autophosphorylation, which causes increased cellular proliferation and survival.[8] Recently, it has been shown that there is an association between macrocytosis (mean corpuscular volume [MCV] $\geq$100 fL) and improved survival in solid tumor patients treated with oral TKIs with potent c-KIT activity.[9,10] This suggests that macrocytosis could be a predictive biomarker of improved survival. However, the positive association between macrocytosis and survival has never been evaluated in chronic phase CML patients treated with TKIs.

There is an unmet clinical need to identify and validate predictive biomarkers of response to TKIs so that clinicians can select the optimal TKI and dose for each CML patient. The overall objective of this study was to evaluate macrocytosis (MCV >100 fL) as a predictive biomarker of improved MMR at 365 days for patients treated with one of the four TKIs that have been approved by the U.S. Food and Drug Administration for the treatment of chronic phase CML: imatinib, dasatinib, or nilotinib, bosutinib. To evaluate this gap in knowledge, we conducted a single-institution retrospective cohort study where data was collected from patients treated with any of the four TKIs used for chronic phase CML. We evaluated associations between treatment-emergent macrocytosis (MCV >100 fL) and clinical outcomes: CHR at 30 days, EMR at 90 days, MMR at 365 days, and adverse events.

Patients and Methods

Data extraction and cohort characterization

This was a single-institution retrospective study of 110 UNCMC patients with a chronic phase CML diagnosis who were treated with a TKI between January 1, 2010 to April 15, 2018 (UNC IRB 17-2003). The Carolina Data Warehouse for Health (CDW-H), which is a central data repository containing clinical, research, and administrative data sourced from UNC Health Care System, was queried to identify patients who would be eligible for this study. Data was manually extracted from the UNCMC electronic medical record (Epic@UNC) for those patients meeting the inclusion criteria. Data extracted from Epic@UNC included: patient baseline clinical and demographic information, TKI treatment details, laboratory values for the first 12 months of TKI treatment and information related to molecular response (i.e., *BCR-ABL1* transcript). Hematologic parameters such as hemoglobin (Hgb), MCV, and red cell distribution width (RDW) were collected at baseline, 1 month, 3 months, 6 months, 9 months and 12 months of treatment or until treatment TKI discontinuation date (if it occurred with a year of treatment start date). Treatment-emergent macrocytosis was defined as an MCV that started ≤100 fL but increased to an MCV >100 fL at any point during treatment.[9,10]

Patients & Endpoints

Patients were included if they were ≥18 years old, treated at UNCMC between Jan 1, 2010 and April 15, 2018, diagnosed with chronic phase CML, initiated on a TKI for at least 3 months. Patients were excluded if they were pregnant, prescribed concomitant chemotherapeutic agents (hydroxyurea or omacetaxine), had additional primary solid or hematologic malignancies, or acute myeloid leukemia, acute lymphocytic leukemia, Ph+ acute lymphocytic leukemia or CML in blast phase or accelerated phase. The primary endpoint was incidence of CHR at 30 days which was defined as this WBC $<10x10^9$/L 30 days after the initiation of the TKI. Per the ELN Guidelines, CHR was defined as WBC $<10x10^9$/L 30 days after TKI initiation, EMR was defined as BCR-ABL ≤ 10% 90 days after the TKI initiation and MMR was defined as BCR-ABL≤0.1% 365 days after TKI initiation.[7] Secondary endpoints included time to CHR, EMR, time to MMR, EMR at 90 days and MMR at 365 days.

Statistical analyses

Descriptive statistics were used to characterize the patient population and categorical variables including sex, race, ethnicity and prescribed TKI were summarized as counts and percentages. Continuous variables including age, line of therapy, starting dose, and baseline values for LFTs, MCV, RBC, RDW and Hgb were summarized as medians (with range), or as means (with standard deviation), as appropriate. A Fisher's exact test was used to evaluate the incidence of CHR at 30 days, EMR at 90 days, MMR at 365 days. For these same endpoints, logistic regression was used to derive odds ratios (OR) and 95% confidence intervals (CIs). Time to event analyses were used for time to CHR, time to EMR and time to MMR and were estimated by log-rank tests using Kaplan-Meier curves. For time to event analyses, Cox Proportional Hazard models will be used to estimate multivariable time-to-event survival analyses, and will be used to derive hazard ratios (HR) and 95% CIs. Multivariable analyses were unable to be performed given the low incidence rate of treatment-induced macrocytosis. Thus, all inferential statistical testing were two-sided, and unadjusted $P<0.05$ was deemed significant. All statistical analyses were performed using SAS JMP Pro 14.0.0 (SAS Institute, Cary, NC, USA) and Kaplan Meier plots were generated using GraphPad Prism version 8.2 (GraphPad, San Diego, CA).

Results

Study Population and baseline characteristics

A total of 110 patients with chronic phase CML treated with TKIs at UNCMC were included in the study (Figure 1). The most commonly prescribed TKIs were dasatinib (n=47) and imatinib (n=34). The median age of CML diagnosis was 51 years-old and the median age TKI initiation was 53 years-old. The study cohort was comprised of 47% male and 57% female, while 64% of patients were White and 30% were Black. Most patients in the cohort were still prescribed their first- or second-line of TKI (48% and 32%, respectively).

Seven of the 110 patients (6.4%) in the cohort developed macrocytosis during TKI treatment. Table 1 provides baseline clinical and demographic information for the patient cohort, and include differences in baseline characteristics between patients with MCV >100 fL during treatment versus patients who MCV $\leq$100 fL. Of note, five of the seven patients (71.4%) who developed MCV >100 fL were male, compared to a study cohort comprised of only 47% men. Additionally, 71.4% of patients who developed MCV >100 fL were on their first-line of TKI treatment compared to 48.2% in the entire cohort.

Macrocytosis and Clinical Endpoints

The clinically relevant endpoints of CHR, EMR, and MMR were evaluated. A total of 90 patients (82%) were eligible to be evaluated for the incidence of CHR. Significant associations between treatment-emergent macrocytosis and both percentage of patients who achieved CHR at 30 days and median days to CHR and were observed (Table 2 and Figure 2-3). Among the patients who experienced treatment-emergent macrocytosis, 87.5% achieved CHR within 30 days, compared to 39.0% of patients who did not (OR=10.9, 95% CI 1.76-125.2; *P*= 0.02; Table 2 and Figure 2). Moreover, patients who experienced treatment-emergent macrocytosis had a significantly shorter time to CHR that patients who did not experience macrocytosis (median 26 days versus 32 days; HR=2.58, 95% CI 1.49-8.40; *P* =0.009; Figure 3).

A total of 67 patients were eligible to be evaluated for the incidence of EMR (60.9%). Significant associations were not observed between treatment-emergent macrocytosis and both percentage of EMR at 90 days

and median days to EMR (Table 2 and Figure 4-5). Among the patients who experienced treatment-emergent macrocytosis, 25% achieved EMR at 90 days compared to 28.9% of patients who did not (OR=0.86, 95% CI [0.16-4.04]; *P*=0.99). In addition, there was no observed difference in time to EMR among patients who experienced treatment-emergent macrocytosis versus those who did not (median 116 days versus 102 days; HR=0.79, 95% CI 0.31-2.00; *P*=0.80).

A total of 79 patients were eligible to be evaluated for the incidence of MMR (71.8%). Significant associations were not observed between treatment-emergent macrocytosis and both percentage of MMR at 365 days and median days to MMR (Table 2 and Figure 6-7). Among the patients who experienced treatment-emergent macrocytosis, 33.3% of patients achieved MMR at 365 days compared to 52.1% of patients who did not (OR=0.46, 95% CI 0.08.210; *P*=0.43). In addition, patients who experienced treatment-emergent macrocytosis had a median 368 days to MMR compared to 212 days in patients with MMR $\leq$ 100 fL (HR = 0.58, 95% CI 0.18-1.54; *P*=0.64).

Discussion

Currently, there are a lack of predictive biomarkers used clinically to direct TKI therapy decision making in chronic phase CML. The goal of this study was to evaluate the association between treatment-emergent macrocytosis and clinically relevant endpoints in CML patients prescribed orally administered TKIs, such as CHR, EMR, MMR, and CMR. This retrospective study was the first step toward evaluating macrocytosis as a predictive biomarker of drug response and improved clinical outcomes in CML.

The most important finding from this study was that a significant association was observed between patients who develop MCV >100 fL during TKI treatment in both the days to complete hematologic response and the incidence of complete hematologic response compared to patients with MCV $\leq$100 fL during TKI treatment. One potential covariate to explain the association between macrocytosis and both CHR evaluations could be whether the TKI was prescribed in the first-line. In this study, 71.4% of patients in the MCV >100 fL group were prescribed first-line therapy, compared to only 46.6% in the MCV $\leq$100 fL group. CHR is most frequently observed in first-line therapy, when patients are first diagnosed with CML and likely have elevated WBC and

platelets.[11] Patients commonly switch TKIs based on toxicities unrelated to blood counts and hematologic responses are not typically observed as platelets and white blood cells commonly already at normal values on baseline. Despite a numerical higher percentage of patients with MCV >100 fL being prescribed their TKI in the first-line, a significant difference was not observed (*P*=0.24); however, this could be attributed to the modest number of patients in the MCV >100 fL arm. Additionally, significant associations between treatment-emergent macrocytosis and EMR and MMR were not observed. Results of this study are significant as they support the need for larger patient populations studies to confirm the association between treatment-emergent macrocytosis and CHR, as well as further investigate the association between macrocytosis and molecular response (EMR and MMR).

The incidence of macrocytosis in the study cohort was low (6.4%), compared to previously published studies in solid tumor patients, which observed a range of approximately 19.0-31.5% of patients who experienced treatment-emergent macrocytosis.[10,12,13] This could be attributed to differences in the pathophysiology of chronic myeloid leukemia compared to solid malignancies from which the association has been observed such as gastrointestinal stromal tumor and renal cell carcinoma.[14] Mutations in c-KIT are commonly implicated in gastrointestinal stromal tumor and renal cell carcinoma, but have not been observed in chronic myeloid leukemia.[14] Perhaps the macrocytosis associated adverse effect of c-KIT is not as commonly observed because c-KIT mutations are not as common in CML. Another possibility is in the underlying cause of CML, a hematologic malignancy originating in hematopoietic stem cells.[1,15,16] Given that CML is due to mutations in hematologic progenitor cells, perhaps the c-KIT expression on hematopoietic progenitor cells is not expressed due to mutations in the hematopoietic progenitor cells implicated in CML.[16] The mechanism behind the association between c-KIT targeting TKIs, macrocytosis and clinical outcomes has not yet been fully elucidated; however, potential clues are available in the expression pattern of c-KIT. The receptor tyrosine kinase, c-KIT is involved in various essential cellular and biological processes, such as fertility, cellular homeostasis and melanogenesis.[8] In cancer, it has been postulated that overexpression and gain of function mutations of *CKIT* lead to a c-KIT protein capable of autophosphorylation, resulting in constitutive c-KIT activation and ultimately causing increased cellular proliferation and survival.[8] Multiple studies have observed an association between higher MCV and mean cell

hemoglobin and longer progression-free survival in patients with solid tumors taking TKIs with c-KIT inhibition.[9,10] One hypothesis to explain this association in the solid tumor setting could be that that TKI-induced macrocytosis is due to disruption in cell maturation due to c-KIT inhibition, leading to the release of large, immature erythrocytes into the bloodstream. [12,17] However, in CML c-KIT inhibition in the hematologic progenitor cells may not be observed as CML itself is derived from mutations in hematologic progenitor cells, possibly explaining the low incidence of macrocytosis.

Future studies, which enroll larger patient cohorts, are needed to better understand the relationship between macrocytosis and clinical endpoints in CML. This was a pure discovery cohort, and all results derived from our analyses requires validation with an independent external cohort of patients. Given the novelty of our study hypothesis, we did not have the ability to estimate power so we assembled the largest population possible. Unfortunately, our patient population was small with n=110 as well the incidence of macrocytosis was low n=7 (6.4%).

Given the retrospective nature of this study, several limitations were encountered. First, a causal relationship between macrocytosis and improved CHR could not be evaluated, and only an association between these two variables could be identified. Additionally, data was collected solely from clinician notes and patient charts in Epic@UNC, which could have possibly led to misclassification bias. Subjective data (such as adverse events and reasons for TKI discontinuation) was entirely dependent on the thoroughness of clinician notes, and key pieces of information may have been missing. Furthermore, the low incidence rate of macrocytosis (n=7) did not allow for identification of potentially impactful covariates, and thus multivariable analyses were not performed. Additionally, we were not able to schedule study visits, order labs, and thus even our objective data was subject to missingness and potential bias. Other limitations include the low incidence of patients who were on their first line of therapy (n=53). Last, as this was a single center study, these results may only have internal validity and may not be generalizable in other settings. Given that roughly 50% of the patients observed had previously lines of therapy, a significant change in molecular response and hematologic response was unable to be observed given previously lines of TKI treatment.

In conclusion, this study observed a significant association between treatment-emergent macrocytosis and both the incidence of CHR at 30 days and time to CHR. An association between treatment-emergent macrocytosis and MMR or EMR was not observed. This study was the first study to evaluate the association between treatment-emergent macrocytosis and improved clinical endpoints in a hematologic malignancy. Future studies with a larger patient cohort are warranted to better understand the associations between treatment-emergent macrocytosis and outcomes (i.e., CHR, EMR, MMR and CMR), as well as confirm the association between treatment-emergent macrocytosis and TKI-induced toxicities.

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Tables and Figures

Table 1. Patient Baseline and Demographic Characteristics.

Variable	Whole Cohort (n=110)	MCV >100 fL (n=7)	MCV ≤100 fL (n= 103)	P-value
Age, median years (range)	51 (22-88)	55 (39-80)	50 (22-88)	0.11
Sex, n (%)				0.13
Male	47 (42.7)	5 (71.4)	42 (40.8)	
Female	63 (57.3)	2 (28.6)	61 (59.2)	
Race, n (%)				0.12
White	84 (76.3)	4 (57.1)	80 (77.7)	
Black	17 (15.5)	1 (14.3)	16 (15.5)	
Other	9 (8.2)	2 (28.6)	7 (6.8)	
Ethnicity, n (%)				
Hispanic	4 (3.6)	1 (14.3)	3 (2.9)	0.23
Non-Hispanic	106 (96.4)	6 (85.7)	100 (97.1)	
TKI, n (%)				0.33
Imatinib	34 (30.9)	2 (28.6)	32 (31.1)	
Dasatinib	47 (42.7)	5 (71.4)	42 (40.8)	
Nilotinib	13 (11.8)	0 (0)	13 (12.6)	
Bosutinib	16 (14.5)	0 (0)	16 (15.5)	
Line of Therapy				0.50
1	53 (48.2)	5 (71.4)	48 (46.6)	
2	35 (31.8)	2 (28.6)	33 (32)	
3	15 (13.6)	0 (0)	15 (14.6)	
≥ 4	7 (6.4)	0 (0)	7 (6.8)	
TKI Starting Dose, mean mg (SD)				
Imatinib	391.18 (37.88)	400.0 (0)	390.0 (37.85)	>0.99
Dasatinib	94.26 (17.66)	100.0 (0)	93.41 (18.79)	>0.99
Nilotinib	557.69 (135.16)	N/A	566.67 (129.86)	N/A
Bosutinib	375 (77.46)	N/A	375 (77.46)	N/A
Baseline Laboratory Parameters, median (range)				
Alk Phos (U/L)	80 (42-447)	75 (54-89)	80 (42-447)	0.50
ALT (U/L)	30 (13-136)	30.5 (18-49)	30 (13-136)	0.99
AST (U/L)	30 (11-80)	35 (17-69)	29 (11-80)	0.17
Tbili (mg/dL)	0.5 (0.1-2.1)	0.6 (0.2-1.6)	0.5 (0.1-2.1)	0.43
CrCl (mL/min)	88.36 (13.79-183.8)	82.7 (32.9-153.3)	87.54 (13.79-183.8)	0.95
SCr (mg/dL)	0.83 (0.5-5.31)	1.0 (0.50-1.91)	0.82 (0.54-5.31)	0.94
Weight (kg)	86.8 (38.1-173.9)	94.9 (69.6-112.9)	86.25 (38.1-173.9)	0.55
Baseline Hematologic Parameters, median (range)				
MCV (fL)	90.0 (76-106)	95.5 (88-99)	89.9 (76-106)	0.06
RBC (10^{12} cells/L)	4.125 (1.89-5.4)	3.75 (3.11-5.11)	4.14 (1.89-5.40)	0.62
RDW (%)	16 (11.8-25.2)	17.4 (14.6-25.2)	16.0 (11.8-23.5)	0.11
Hgb (g/dL)	12.1 (5.6-15.7)	12.0 (8.5-14.5)	12.1 (5.6-15.7)	0.51

Baseline and demographic characteristics were collected for patient cohort through UNC electronic medical record (Epic@UNC). Percentages are included for representation of the population. Differences in baseline characteristics between patients who develop MCV >100 fL during TKI treatment and patients who do not is also depicted.

P-values are unadjusted. Significant results ($P<0.05$) are bolded.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alk Phos, alkaline phosphatase; CrCl, creatinine clearance; Hgb, hemoglobin; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red blood cell distribution width; SCr, serum creatinine; SD, standard deviation; Tbili, total bilirubin; TKI, tyrosine kinase inhibitor

Table 2. Evaluation of TKI efficacy endpoints.

	Whole Cohort (n=110)	**MCV >100 fL (n=7)**	**MCV ≤100 fL (n=103)**
Achieved CHR at 30 days (n=90)			
Number (%)	38 (42.7)	6 (85.7)	32 (39%)
OR, 95% CI	10.9 (1.76-125.2); ***P*=0.02**		
Achieved EMR at 90 days (n=67)			
Number (%)	19 (28.4)	2 (33.3)	17 (27.9)
OR, 95% CI	0.86 (0.16-4.04); *P*=0.99		
Achieved MMR at 365 days (n=79)			
Number (%)	40 (50.6)	2 (33.3)	38 (52.1)
OR, 95% CI	0.46 (0.08-2.10); *P*=0.43		

For eligible patients, CHR at 90 days, EMR at 90 days and MMR at 365 are depicted. Patients were not eligible for evaluation if they had already met endpoints at baseline.

P-values are unadjusted. Significant results ($P<0.05$) are bolded.

Abbreviations: CHR, complete hematologic response; CI, confidence interval; EMR, early molecular response; MMR, major molecular response; MCV, mean corpuscular volume.

Figure 1. Study Schematic. A total of 962 potentially eligible patients were identified. Study medications included imatinib, dasatinib, nilotinib and bosutinib. A total of 110 patients met the inclusion criteria and comprised of the final study cohort. *indicates either incarcerated patient (n=3), initiated TKI while <18 (n=3), prescribed hydroxyurea (n=7). Abbreviations: CML, chronic myeloid leukemia; MCV, mean corpuscular volume; TKI, tyrosine kinase inhibitor.

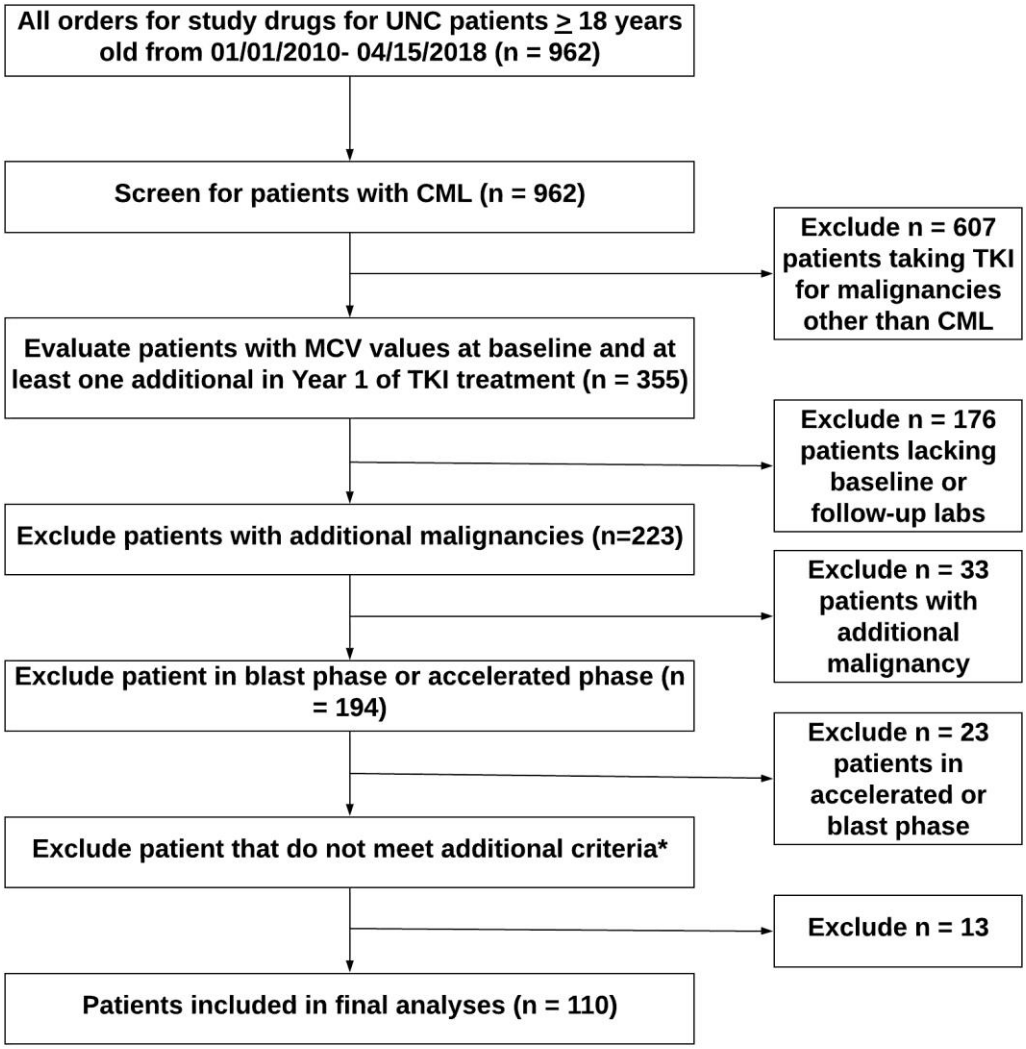
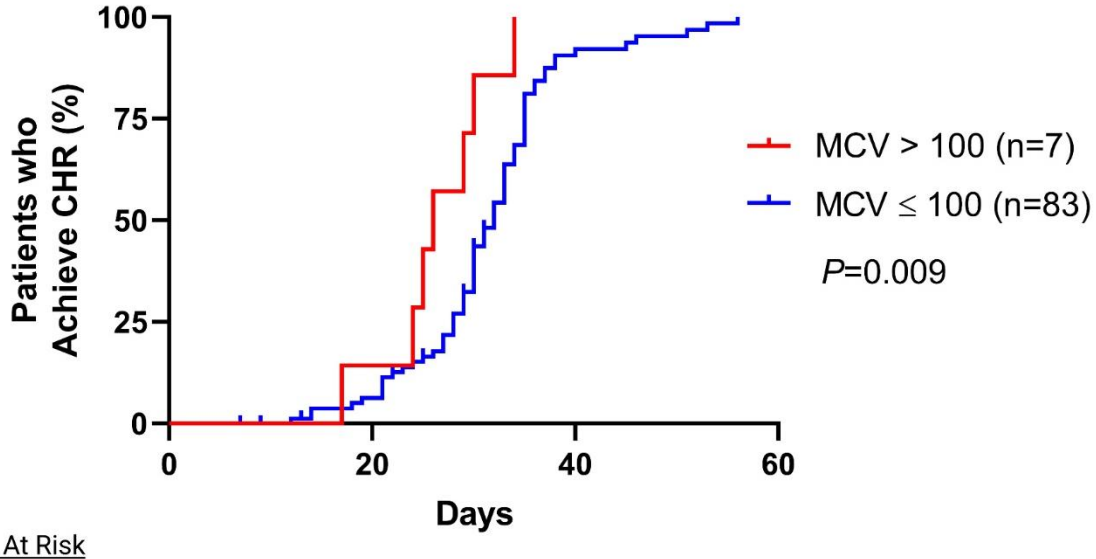


Figure 2. Time to complete hematologic response. This figure shows the cumulative incidence of patients who achieve CHR over time. Median days to CHR was 26 for MCV >100 fL (n=7), and 32 for MCV ≤100 fL (n=83). Abbreviations: CHR, complete hematologic response; MCV, mean corpuscular volume.



Number At Risk				
MCV >100 fL	0	1	7	7
MCV ≤100 fL	0	8	77	83

Figure 3. Complete hematologic response at 30 days. This figure shows the percentage of patients who achieved CHR by 30 days. A total of 85.7% for MCV >100 fL patients achieved CHR by 30 days (n=7) versus 39.0% for MCV ≤ 100 fL patients (n=83). Abbreviations: CHR, complete hematologic response; MCV, mean corpuscular volume.

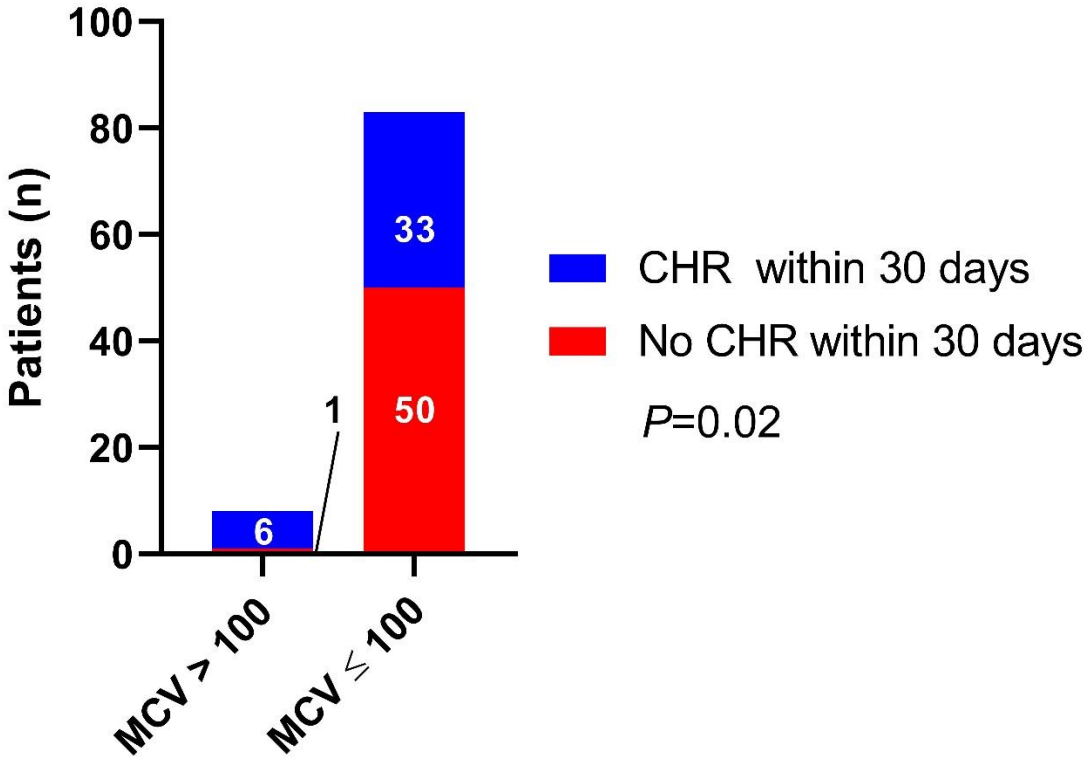
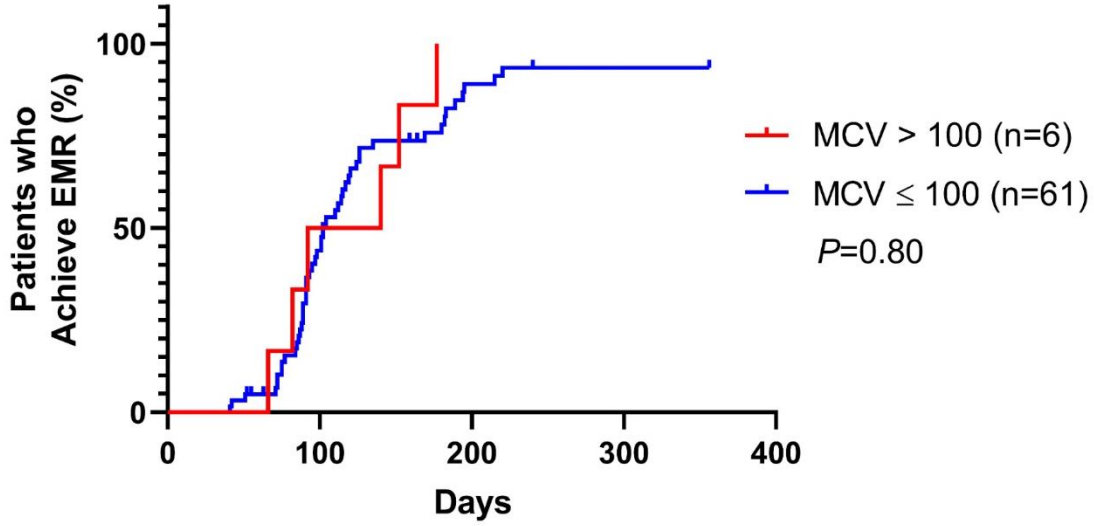


Figure 4. Time to early molecular response. This figure shows the cumulative incidence of patients who achieve EMR over time. Median days to EMR was 116 for MCV >100 fL (n=6), and 102 for MCV ≤100 fL (n=61). Abbreviations: EMR, early molecular response; MCV, mean corpuscular volume.



Number At Risk					
MCV >100 fL	0	3	6	6	6
MCV ≤100 fL	0	30	56	60	61

Figure 5. Early molecular response at 90 days. This figure shows the percentage of patients who achieved EMR by 90 days. A total of 33.3% for MCV > 100 fL patients achieved EMR by 90 days (n=7) versus 27.9% for MCV ≤ 100 fL patients (n=61). Abbreviations: EMR, early molecular response; MCV, mean corpuscular volume.

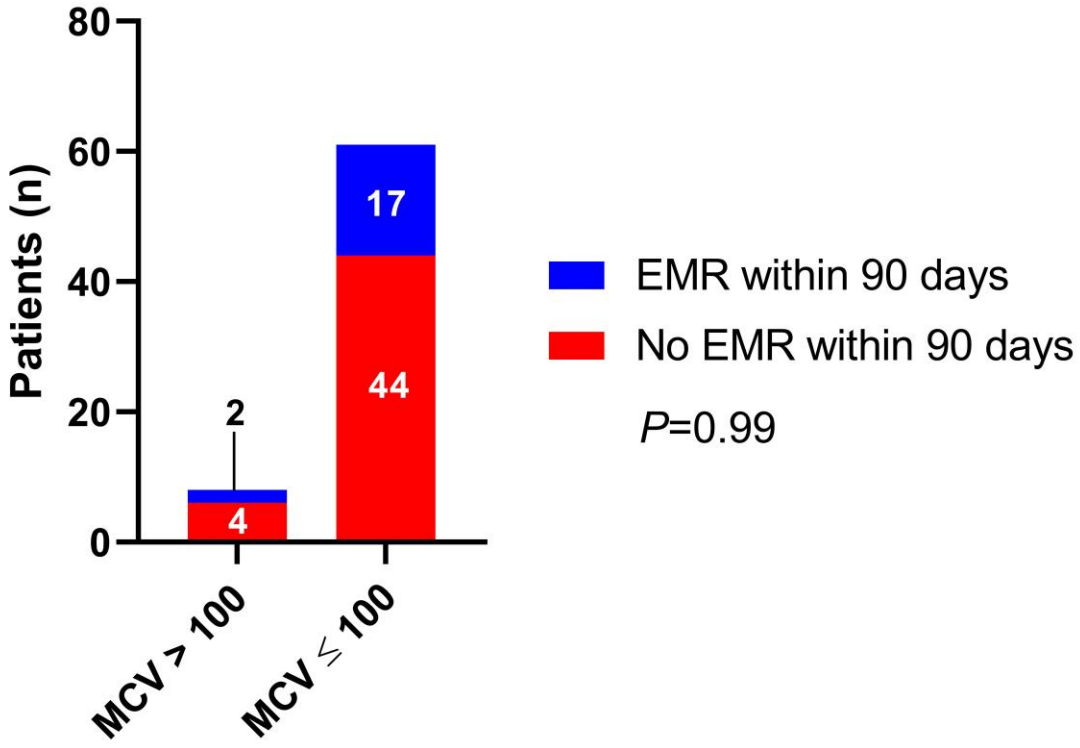
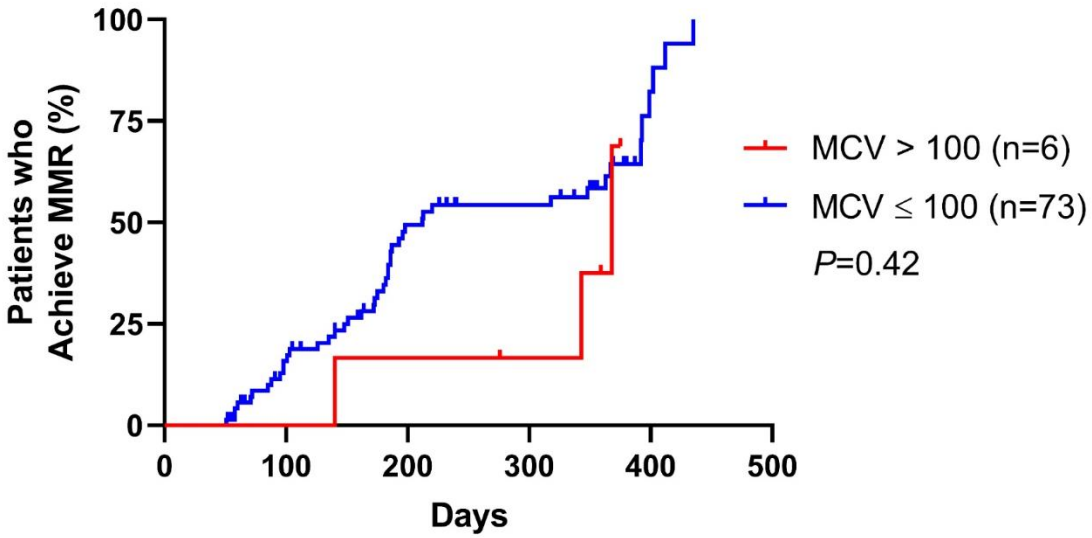


Figure 6. Time to major molecular response. This figure shows the cumulative incidence of patients who achieved MMR over time. Median days to MMR was 368 for MCV >100 fL (n=6), and 212 for MCV ≤100 fL (n=73). Abbreviations: MMR, major molecular response; MCV, mean corpuscular volume.



Number At Risk						
MCV >100 fL	0	0	1	2	6	6
MCV ≤100 fL	0	16	42	50	70	73

Figure 7. Major molecular response at 365 days. This figure shows the percentage of patients who achieved MMR by365 days. A total of 33.3% for MCV > 100 fL patients achieved MMR by 365 days (n=6) versus 52.1% for MCV < 100 fL patients (n=73). Abbreviations: MMR, major molecular response; MCV, mean corpuscular volume.