A retrospective analysis of upfront treatment strategies in chronic myelomonocytic leukemia: impact on survival and response patterns

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Abstract

In a retrospective analysis of 457 Mayo Clinic patients (median age 72 years) with chronic myelomonocytic leukemia (CMML) (proliferative 38%; CMML-2 15%), overall survival (OS), calculated from time of diagnosis, was not differentially affected by treatment exposure to: i) either cytotoxic or non-cytotoxic drugs (i.e., untreated; N=155; median 29 months); ii) non-cytotoxic drugs (N=95; median 25 months); iii) hydroxyurea (HU; N=102; median 23 months) or hypomethylating agent (HMA; N=78; median 35 months), as the first-line choice of cytotoxic therapy; or iv) cytotoxic drugs other than HU or HMA (N=27; median 18 months) (P=0.2). Blast transformation (BT) was more frequent in patients exposed to cytotoxic (26%) *versus* non-cytotoxic (11%) drugs (P<0.01), confirmed in multivariable analysis (HR [Hazard Ratio] 2.0; 95% Confidence Interval [CI]: 1.2-3.3) that accounted for other risk factors. Comparison of patients receiving HU or HMA favored HMA for control of leukocytosis (P<0.01), anemia (P=0.02), and thrombocytopenia (P=0.06); however, there was no difference in OS (P=0.3) or BT-free survival (P=0.7) between the two treatment arms. *RUNX1* mutation was associated with lower response rates in leukocytosis (P=0.03) and thrombocytopenia (P=0.03) in HU/HMA treated patients. Allogeneic stem cell transplantation was undertaken in 49 patients with median post-transplant survival of 69 months. Our study confirms that current drug therapy in CMML has no impact on OS. Instead, it suggests a significant association between BT and the need for cytotoxic drug therapy. Our observations regarding higher response rates with HMA *versus* HU are also in line with a previously published controlled study.

Introduction

Chronic myelomonocytic leukemia (CMML) is a hematopoietic stem cell-derived myeloid malignancy that is formally defined by a set of diagnostic criteria that are similar between two major classification systems: the International Consensus Classification (ICC)[1] and the World Health Organization (WHO) classification, 5th edition;[2] i) presence of peripheral blood (PB) absolute monocyte count (AMC) of ≥0.5x10^9/L, in association with PB monocyte percentage of ≥10% of the total white blood cell count (WBC); ii) presence of an abnormal karyotype, a myeloid neoplasm-associated mutation, or AMC ≥1.0x10^9/L, along with morphologic evidence of dysplasia; and iii) absence of any other myeloid malignancy, as defined by the aforementioned two classification systems, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions.[1,2] Morphologic blast-based subcategories of CMML include CMML-1 (<5% PB and <10% BM blasts/promonocytes) and CMML-2 (5-19% PB or 10-19% bone marrow [BM] blasts/promonocytes, or Auer rods). In addition, myelodysplastic (CMML-MD; leukocyte count <13x10^9/L), and myeloproliferative (CMML-MP; leukocyte count ≥13x10^9/L) subtypes effectively stratify for outcomes, based on the presenting WBC.[1,2]

Treatment strategies in CMML are not standardized due to the disease's heterogeneity, which encompasses features of both MDS and MPN.[3] The contemporary treatment approach relies on the strategic use of hydroxyurea (HU)

and hypomethylating agents (HMA).[4,5] HU is often used in CMML-MP in order to control leukocytosis and alleviate constitutional symptoms, splenomegaly, or extramedullary hematopoiesis.[6] HMA therapy might induce responses in CMML-MD with cytopenic features.[4] In a recently reported DACOTA[7] phase III clinical trial comparing decitabine (DAC) to HU in patients with high-risk CMML-MP, the former resulted in significantly higher response rates (63% *vs*. 35%; *P*<0.01) but with increased treatment-related mortality, negating an advantage on event-free (12.1 *vs*. 10.3 months; *P*=0.27) or overall (18.4 *vs*. 21.9 months) survival, respectively. Furthermore, despite transient hematologic and symptomatic control, neither HU nor HMA has been shown to control the genetic evolution of CMML, which is the hallmark of disease progression.[8,9] Blast transformation (BT) remains an inherent risk in patients with CMML (incidence of 15-29%)[10-12] and is associated with a significantly shorter survival.[13] Current CMML-directed therapies, other than HU or HMA, include erythropoiesis-stimulating agents (ESA)[14] and corticosteroids.[5,15] The current study aims to evaluate the impact of these and other CMML-directed therapies on overall survival (OS), blast-transformation free survival (BTFS), and indication-specific responses.

Methods

The current retrospective study was conducted under an institutional review board approved minimum risk protocol that allowed retrospective collection and analysis of data from patient records. The study population consisted of 457 patients seen at the Mayo Clinic, Minnesota, Florida, and Arizona, USA, between the years 1994 and 2024. Diagnostic criteria were according to the ICC and confirmed by central review (IRB 12-003574).[1] Cytogenetic results were reported according to the International System for Human Cytogenetic Nomenclature.[16] Anemia was defined as "severe" (transfusion requiring or hemoglobin <8 g/dL in women or <9 g/dL in men) or "moderate" (hemoglobin 8 to <10 g/dL in women or 9 to <11 g/dL in men).

Because of the retrospective design of the current study, utilization of formal response criteria could not be accurately applied. Instead, response criteria used in the current study were as follows: i) leukocytosis: "response" indicated reduction of white blood cell count (WBC) to within the normal reference range (4.0-12x10^9/L); ii) anemia: "response" indicated either resolution of transfusion need for at least three months or, in non-transfusion dependent patients, an increase in hemoglobin level of at least 1.5 g/dL sustained for at least three months; iii) thrombocytopenia: "response" applied to only patients with platelet count of <100x10^9/L at baseline and indicated a >50% increase in platelet count along with a minimum platelet count of 20x10^9/L; iv) splenomegaly: "response" applied to only patients with baseline spleen size of >5 cm palpable to below the left costal margin and indicated either the spleen becoming non-palpable or a >50% reduction in size for baseline spleen size of >10 cm below the left costal margin. The designation of drugs used for treatment into "cytotoxic" and "non-cytotoxic" agents was mostly based on mechanism of action.

Statistical analyses considered clinical and laboratory data collected at the time of initial diagnosis/referral. χ^2 test, ANOVA /*t* test, and correlation analyses were systematically used to compare the clinical and laboratory parameters, assess the treatment response, and calculate the blast-transformation rates. The Kaplan-Meier method was used to construct time-to-event curves, which were compared by the log-rank test. Multivariable logistic regression analysis was used to adjust for confounding variables. Cox regression analysis was applied to identify risk factors for OS and BTFS. Cumulative incidence function (CIF) analysis was performed to account for death as a competing risk, with Gray's test used to evaluate its numerical significance. In survival analyses, patients were censored at the time of allogenic stem cell transplantation (ASCT) for OS, at BT for BTFS, and additionally at death in CIF analysis. Statistical analyses were conducted using JMP Pro 17.0.0 software (SAS Institute, Cary, NC, USA) and Bluesky Statistics Software (Worldwide Headquarters, Chicago, IL, USA).

Results

Presenting clinical and laboratory characteristics

A total of 457 Mayo Clinic patients with CMML were included in the current study (Table 1): median age 72 years (range 24-95); males 68%; CMML-MP 38%; CMML-MD 62%; CMML-1 85%; CMML-2 15%; therapy-related 13%; CMML-specific prognostic scoring system (CPSS)-mol[17] risk category low 17%, intermediate-1 24%, intermediate-2 37%, and high 22%. Median WBC was 11.7x10^9/L (range 1.8-185.7), AMC 2.3x10^9/L (range 0.5-51), platelet count 95x10^9/L (range 6-1257), and hemoglobin levels in red blood cell (RBC) non-transfused patients 11.9 g/dL (range 7.9-16.9). RBC transfusion need at diagnosis was documented for 25% of patients; severe anemia as defined above (see Methods section) in 27%; moderate anemia in 16%; PB blast ≥2% in 15%; platelets <100x10^9/L in 54%; and WBC ≥13x10^9/L in 38% (Table 1).

Among treatment groups, patients who received HMA as their first-line cytotoxic drug were more likely to be classified as CMML-2 (*P*<0.01), display higher BM blast percentage (*P*<0.01) or lower platelet count (*P*=0.02), and undergo ASCT (*P*<0.01) (Table 1). Patients who received HU as their first-line cytotoxic drug were more likely to be classified as CMML-MP (*P*<0.01) and display higher leukocyte (*P*<0.01) and absolute monocyte (AMC; *P*<0.01) count. Patients with no documentation of CMML-directed therapy during their clinical course were more likely to be older (*P*<0.01), be classified as CMML-1 (*P*<0.01), present with higher hemoglobin

Table 1. Clinical and laboratory findings of 457 patients diagnosed with chronic myelomonocytic leukemia, stratified by treatment groups.

Variables	All patients N=457	HU N=102	HMA N=78	Other cytotoxic N=27	Other non-cytotoxic N=95	No treatment N=155	*P*
Age, years, median (range)	72 (24-95)	72 (24-90)	70 (44-85)	67 (44-83)	76 (37-90)	74 (31-95)	<0.01#
CMML WHO classification, N (%) CMML-1 CMML-2	 371 (85) 64 (15)	 86 (86) 14 (14)	 57 (73) 21 (27)	 22 (81) 5 (19)	 88 (93) 7 (7)	 136 (88) 19 (12)	-
Transfusion-requiring, N (%)	115 (25)	26 (26)	21 (27)	12 (44)	29 (31)	27 (17)	0.02#
Hemoglobin g/dL, median (range)	11 (6-17)	11 (6-15.5)	11 (6.5-16)	10 (6.4-15)	10.5 (6.4-15.3)	12 (6.4-17)	<0.01#
Platelets $\times 10^9$/L, median (range)	95 (6-1257)	96 (20-820)	76 (6-1257)	97 (13-308)	99 (10-742)	95 (11-726)	0.02#
Platelets $<100\times 10^9$/L, N (%)	248 (54)	52 (51)	50 (64)	14 (52)	48 (51)	84 (54)	0.4
Leukocytes $\times 10^9$/L, median (range)	12 (2-186)	22 (3.2-186)	9.1 (2.3-71)	15 (3.4-94)	6.7 (2.2-36)	9.1 (1.8-166)	<0.01#
Leukocytes $\geq 13\times 10^9$/L, N (%)	172 (38)	66 (65)	23 (29)	14 (52)	30 (34)	39 (25)	<0.01#
Absolute neutrophil count $\times 10^9$/L, median (range)	2.3 (0.5-51)	4 (1-32)	2 (0.5-21)	3 (0.5-38)	2 (0.5-38)	2 (0.5-51)	<0.01#
Absolute monocyte count $\times 10^9$/L, median (range)	6.1 (0-143)	14 (1-143)	4 (0-34)	20 (2-114)	6 (0-63)	4 (0-43)	<0.01#
Blood blast %, median (range)	0 (0-18)	0 (0-18)	0 (0-17)	0 (0-10)	0 (0-15)	0 (0-15)	<0.01#
Blood blast ≥2%, N (%)	68 (15)	26 (26)	14 (18)	9 (33)	8 (8)	11 (7)	<0.01#
Bone marrow blast %, median (range)	3 (0-19)	3 (0-18)	4 (0-18)	3 (0-17)	2 (0-18)	3 (0-19)	<0.01#
Bone marrow blast ≥10%, N (%)	10 (2)	2 (2)	3 (4)	1 (4)	2 (2)	2 (1)	0.77
Cytogenetics, N (%) Normal karyotype Abnormal karyotype	 336 (75) 115 (25)	 74 (73) 27 (27)	 61 (78) 17 (22)	 18 (67) 8 (30)	 68 (71) 26 (29)	 116 (75) 35 (23)	0.79
Anemia severity;* N (%) Moderate anemia Severe anemia	 81 (18) 115 (25)	 12 (12) 28 (28)	 13 (17) 21 (27)	 5 (19) 11 (41)	 20 (21) 27 (28)	 36 (23) 20 (13)	<0.01#
CPSS-mol** risk category, 449 evaluated, N (%) Low risk Intermediate-1 Intermediate-2 High risk	 75 (17) 109 (24) 167 (37) 100 (22)	 12 (12) 9 (9) 41 (41) 28 (28)	 14 (18) 16 (21) 19 (24) 24 (31)	 3 (11) 4 (15) 8 (30) 8 (30)	 18 (19) 22 (23) 29 (31) 17 (18)	 40 (26) 28 (18) 36 (23) 23 (15)	<0.01#
NGS mutations, N (%) *TET2* *ASXL1* *SRSF2* *NRAS* *RUNX1* *KRAS* *U2AF1* *PHF6* *DNMT3A* *SETBP1* *EZH2* *IDH1/2* *JAK2* *SF3B1* *PTPTN11* *ZRSR2* *KIT* *CBL* *CEBPA* *BCOR* *TP53*	 219 (48) 209 (46) 193 (42) 73 (16) 72 (16) 42 (9) 37 (8) 36 (8) 34 (7) 33 (7) 26 (5) 26 (5) 21 (4) 20 (4) 20 (4) 18 (4) 18 (4) 16 (3) 13 (3) 12 (2) 10 (2)	 51 (51) 55 (54) 50 (50) 18 (18) 16 (16) 11 (11) 10 (10) 2 (2) 8 (8) 15 (15) 10 (10) 0 (0) 9 (9) 5 (5) 2 (2) 3 (3) 5 (5) 4 (4) 4 (4) 3 (3) 4 (4)	 41 (53) 39 (50) 33 (42) 15 (19) 19 (24) 5 (6) 7 (9) 8 (10) 9 (12) 2 (3) 6 (8) 1 (2) 2 (3) 3 (4) 6 (8) 5 (6) 2 (3) 3 (4) 1 (2) 3 (4) 3 (4)	 11 (41) 12 (45) 9 (33) 7 (26) 4 (15) 2 (7) 2 (7) 1 (4) 3 (11) 1 (4) 0 (0) 0 (0) 1 (4) 1 (4) 2 (7) 1 (4) 3 (11) 1 (4) 0 (0) 3 (11) 0 (0)	 35 (37) 42 (44) 37 (39) 11 (12) 8 (8) 10 (11) 7 (7) 9 (9) 7 (7) 8 (8) 2 (2) 3 (3) 2 (2) 6 (6) 7 (7) 4 (4) 4 (4) 3 (3) 2 (2) 0 (0) 2 (2)	 81 (52) 61 (39) 64 (41) 22 (14) 25 (16) 14 (9) 11 (7) 16 (10) 7 (4) 7 (4) 8 (5) 2 (1) 7 (4) 5 (3) 3 (2) 5 (3) 4 (2) 5 (3) 6 (4) 3 (2) 1 (0.6)	 0.11 0.20 0.51 0.35 0.07 0.91 0.94 0.04# 0.36 0.01# 0.05# 0.25 0.20 0.83 0.07 0.80 0.43 0.99 0.50 0.03# 0.23

Continued on following page.

Variables	All patients N=457	HU N=102	HMA N=78	Other cytotoxic N=27	Other non-cytotoxic N=95	No treatment N=155	*P*
Acute myeloid leukemia transformation, N (%)	89 (20)	27 (26)	20 (26)	7 (26)	10 (11)	18 (12)	<0.01#
Allogeneic stem cell transplant, N (%)	49 (11)	8 (8)	19 (24)	5 (19)	5 (5)	12 (8)	<0.01#
Deaths, N (%)	326 (71)	72 (71)	43 (55)	19 (33)	71 (75)	104 (67)	0.08

*Moderate: hemoglobin 8 to <10 g/dL in women and 9 to <11 g/dL in men; Severe: transfusion-dependent or hemoglobin <8 g/dL in women and <9 g/dL in men. **CPSS-mol: chronic myelomonocytic leukemia (CMML)-specific prognostic scoring system that incorporates molecular genetic data. HMA: hypomethylating agents; HU: hydroxyurea; N: number; NGS: next generation sequencing; WHO: World Health Organization. #Statistically significant.

level (*P*<0.01), and be less likely to require RBC transfusion at presentation (*P*<0.02). Table 1 includes these and other details on patients receiving other therapies.

Treatment details and response rates

Hydroxyurea was listed as first-line CMML-directed cytotoxic therapy, at any stage of the disease course, in 102 and HMA in 78 patients; the latter included azacitidine in 32 or decitabine in 46 patients (Table 2). Other cytotoxic drugs were documented as first-line treatment in 29 patients and included HMA + venetoclax (N=11), tagraxofusp (N=2), idarubicin (N=4), etoposide (N=3), daunorubicin (N=2), cyclophosphamide (N=1), purine / pyrimidine analogs (N=5), and telomerase inhibitor (N=1) (Table 2). A total of 112 patients received non-cytotoxic drugs only (Table 2) during their disease course, including ESA (N=58), tyrosine kinase inhibitors (N=19), corticosteroids (N=16), rituximab (N=3), lenalidomide (N=3), thalidomide (N=1), ruxolitinib (N=4), etanercept (N=3), interferon (N=3), G-CSF (N=1), and romiplostim (N=1). No initial or subsequent-line treatment was recorded for 155 (34%) patients.

Table 2. Overview of upfront treatment groups among 457 patients diagnosed with chronic myelomonocytic leukemia.

Treatment group	N
All patients	457
First-line conventional cytotoxic drugs	209
Hydroxyurea or HMA	180
Hydroxyurea alone	102
HMA alone	78
Azacitidine	32
Decitabine	46
Other cytotoxic drugs used as first-line	29
Venetoclax + HMA	11
Tagraxofusp	2
Idarubicin	4
Etoposide	3
Daunorubicin	2
Cyclophosphamide	1
Purine / Pyrimidine analogs	5
Telomerase inhibitors	1
Other non-cytotoxic drugs as exclusive therapy	112
Erythropoiesis-stimulating agents	58
Tyrosine kinase inhibitors	19
Corticosteroids	16
Rituximab	3
Lenalidomide	3
Thalidomide	1
Ruxolitinib	4
Etanercept	3
Interferon	3
G-CSF	1
Romiplostim	1

CMML: chronic myelomonocytic leukemia; HMA: hypomethylating agent; N: number.

The most frequent treatment indication among HMA-treated cases were leukocytosis in 14 (18%), anemia in 11 (14%), and thrombocytopenia in 12 (15%) patients (Table 3). Among HU-treated cases, leukocytosis was the most common indication in 59 (59%) patients, splenomegaly in 8 (8%), and

Table 3. Indications for treatment in patients receiving hydroxyurea or hypomethylating agents as first-line therapy.

Treatment indications	HU N=102 N (%)	HMA N=78 N (%)	*P*
Leukocytosis	59 (59)	14 (18)	<0.01#
Thrombocytosis	5 (5)	10 (13)	0.08
Anemia	3 (3)	11 (14)	0.04#
Thrombocytopenia	3 (3)	12 (15)	0.08
CMML-related systemic manifestations	4 (4)	4 (5)	NA
Splenomegaly	8 (8)	3 (4)	NA
Disease progression	1 (1)	11 (14)	0.02#
Bridge to bone marrow transplant	0 (0)	3 (4)	NA
Palliative care	1 (1)	0 (0)	NA
Not documented	15 (15)	11 (14)	0.4

CMML: chronic myelomonocytic leukemia; HMA: hypomethylating agents; HU: hydroxyurea; N: number; NA: not available. #Statistically significant.

CMML-related systemic manifestations in 4 (4%) patients (Table 3). Response rates in patients receiving HU or HMA as first-line cytoreductive therapy were adjudicated independently for leukocytosis, anemia, thrombocytopenia, and splenomegaly (Table 4). Complete resolution of leukocytosis was achieved in 21 (39%) of 54 evaluable patients treated with HU and in 10 (83%) of 12 evaluable patients with HMA (P<0.01). Median duration of responses was similar at 131 and 129 months (P=0.47). Anemia response was documented in 7 (64%) of 11 evaluable patients treated with HMA and in none of the 3 evaluable patients treated with HU (P=0.02). Response in thrombocytopenia also favored HMA with 5 (42%) of 12 evaluable patients responding *versus* none of the 4 evaluable patients treated with HU (P=0.06). The number of patients evaluable for spleen response was too small to comment on. A number of mutations, including *TET2*, *PHF6*, *ASXL1*, *NRAS*, *PTPN11*, *DNMT3A*, *TP53*, *RUNX1*, *SETBP1*, *U2AF1*, and others, as well as abnormal karyotype, were examined for possible impact on treatment response. Amongst these, only *RUNX1* mutation was associated with lower response rates in leukocytosis (P=0.03) and thrombocytopenia (P=0.03) in HU/HMA treated patients.

Causes for discontinuation of treatment are shown in Table 5.

Overall survival and causes of death

The median duration of follow-up was 27 months (inter-quartile range 11-44 months). During this period, 326 (71%) patients died, 89 (19.5%) experienced BT, and 49 (11%) received ASCT. Causes of death included BT (37%), cardiovascular disease (18%), progressive disease with multiorgan failure (16%), sepsis or other non-respiratory tract infections (13%), pneumonia or other respiratory tract infections (9%), and other (8%), including non-myeloid cancer deaths in 6 patients. Median OS was 25 months with 1-, 2- and 3-year rates of 74%, 53% and 31%, respectively.

Overall survival was not significantly affected by whether or not patients received CMML-directed therapy or what the first-line choice of drug therapy was (Figure 1): i) no treatment (N=155; median 29 months), ii) non-cytotoxic drugs (N=95; median 25 months), iii) HU (N=102; median 23 months), iv) HMA (N=78; median 35 months), and v) other cytotoxic drugs (N=27; median 18 months) (P=0.2). In univariate analysis, patients who received cytotoxic drugs other than HU and HMA as first-line treatment appeared to have a worse OS (HR 1.65; P=0.04) compared to patients without documentation of any treatment, but significance was not sustained during multivariable analysis (P=0.78) that accounted for BLAST risk factors for OS, including WBC ≥13x10^9/L (P<0.01), severity of anemia (P<0.01), and PB blast count ≥2% (P<0.01).[18] More importantly, there was no difference in either OS (P=0.3) or BTFS (P=0.7) in patients treated with HU *versus* HMA. The lack of any significant difference in OS between HU- and HMA-treated patients was confirmed in multivariable analysis (P=0.5) that included WBC ≥13x10^9/L (P<0.01), severity of anemia (P<0.01), PB blast count ≥2% (P<0.01), and diagnosis date before or after 2004 (P=0.2); the latter variable signified commercial availability of HMA (2004 for azacytidine and 2006 for decitabine).

In the 49 patients who underwent ASCT (median age 62 years; range 31-75; 51% females), deaths and BT occurred in 17 and 3 patients after transplant, respectively. Median duration from initial diagnosis to time of transplant was ten months (range

Table 4. Comparative outcomes of response and duration of treatment in patients receiving hydroxyurea or hypomethylating agents as first-line therapy.

Variables	HU N=102	HMA N=78	*P*
Leukocytosis	N evaluable = 54	N evaluable = 12	
Response* N (%)	21 (39)	10 (83)	<0.01#
Median duration of response, days (range)	131 (2-828)	129 (4-303)	0.47
Anemia	N evaluable = 3	N evaluable = 11	
Response** N (%)	0 (0)	7 (64)	0.02#
Median duration of response, days (range)	NA	362 (106-1,893)	NA
Thrombocytopenia	N evaluable = 4	N evaluable = 12	
Response*** N (%)	0 (0)	5 (42)	0.06#
Median duration of response, days (range)	NA	201 (99-362)	NA
Splenomegaly	N evaluable = 8	N evaluable = 3	
Response**** N (%)	1 (13)	2 (67)	0.08
Median duration of response, days (range)	NA	121 (114-128)	NA

*Response: reduction of white blood cell count to within the normal reference range (4.0-12x10^9/L). **Response: either a resolution of transfusion need for at least 3 months in previously transfusion-dependent patients or an increase in hemoglobin level of at least 1.5 g/dL sustained for at least 3 months in transfusion-independent patients. ***Response: assessed only in patients with a baseline platelet count <100×10^9/L and defined as a >50% increase in platelet count, with a post-treatment minimum of ≥20×10^9/L. ****Response: assessed only in patients with a baseline spleen size >5 cm palpable below the left costal margin and defined as either the spleen becoming non-palpable or a >50% reduction in size for those with a baseline spleen size >10 cm below the left costal margin. HMA: hypomethylating agents; HU: hydroxyurea; N: number; NA: not available. #Statistically significant.

0-205), and treatment history prior to ASCT included HMA in 19 (39%) patients, HU in 8 (16%), other cytotoxic drugs in 5 (10%), and no treatment in 12 (25%). Median post-transplant survival was 69 months, with 32 (65%) patients documented to be alive at the time of writing, including 30 (61%) who were disease-free and 2 (4%) with recurrent CMML. Causes of death after ASCT (N=17) included BT (N=10; 59%), progressive CMML (N=3; 17%), graft-*versus*-host disease (N=1; 6%), and unknown (N=3; 18%).

Blast transformation

During a median follow-up for living patients of 21 months from diagnosis, 89 (19.5%) patients experienced BT, with 1-, 2-, and 3-year BT rates of 11.6%, 24%, and 31%, respectively. BT was more frequent among patients who received cytotoxic drugs (26%) compared to those treated exclusively with non-cytotoxic agents as first-line treatment (11%) (P<0.01) (Figure 2). The latter observation was confirmed in multivariable analysis of BTFS (HR 2.0; 95%CI: 1.2-3.3;

Table 5. Causes for discontinuation during first-line therapy stratified by hydroxyurea and hypomethylating agents.

Cause	HU N evaluable = 73 N (%)	HMA N evaluable = 51 N (%)	*P*
Death	19 (19)	7 (9)	0.02#
Switched to another therapy	12 (12)	2 (3)	0.01#
Thrombocytopenia	11 (11)	2 (3)	0.02#
Lost to follow-up	9 (9)	6 (8)	0.4
Anemia	6 (6)	0 (0)	NA
Ineffective control	5 (5)	10 (13)	0.20
Non-hematologic side effect	4 (4)	4 (5)	0.9
Pancytopenia	3 (3)	1 (1)	0.34
Bone marrow transplant	2 (2)	9 (12)	0.06
Transition to hospice	2 (2)	2 (3)	0.9
Remission	0	5 (7)	NA
Blast leukemia	0	3 (4)	NA

HMA: hypomethylating agents; HU: hydroxyurea; N: number; NA: not available. #Statistically significant.

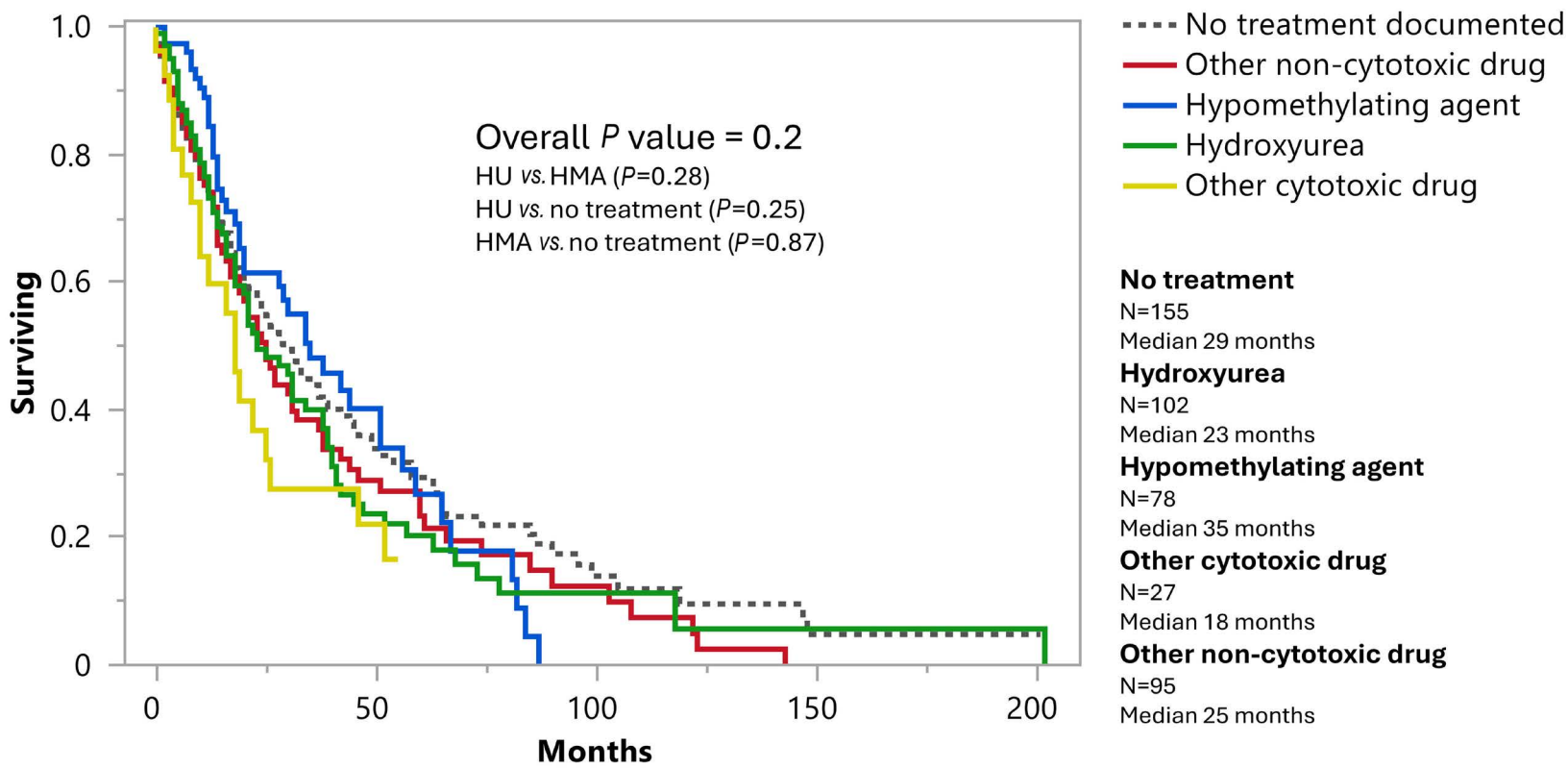

Figure 1. Overall survival comparison among all treatment groups in 457 patients with chronic myelomonocytic leukemia. Kaplan-Meier survival curves are shown; no significant differences in overall survival are observed. HMA: hypomethylating agent; HU: hydroxyurea; N: number.

P<0.01) that accounted for other risk factors for BT, including BM blast ≥10% (HR 4.3), circulating blast ≥2% (HR 2.7), WBC ≥13x10^9/L (HR 1.8), and *ASXL1* mutation (HR 1.7). For a more accurate estimation of this effect, a cumulative incidence function (CIF) analysis was performed with death as a competing risk (Figure 3); 3-year CIF was 22% for HMA, 26% for HU, and 27.1% for other cytotoxic drugs *versus* 10.4% for non-cytotoxic agents (Gray's test: *P*<0.01). A univariate analysis was performed to differentially analyze BTFS among the cytotoxic drugs, observing no differences between HU and HMA (HR 1.1; *P*=0.7) or HU/HMA and other cytotoxic drug therapies (HR: 1.34; *P*=0.46).

Discussion

Chronic myelomonocytic leukemia was formally recognized in the 1970s as a distinct hematologic entity.[19] Its natural history is characterized by progressive leukocytosis, cytopenias, splenomegaly, and BT in 15-29% of cases.[20] Early therapeutic strategies were largely palliative, with a "watch and wait" strategy leading the way.[21] Unfortunately, current treatment in CMML continues to be palliative despite the introduction of HMA (e.g., AZA, DAC) for CMML treatment in the 2000s,[22,23] albeit their approval was originally based on MDS studies which included only a few patients with CMML. At the time of writing, HU and HMA are considered standards of practice treatment in CMML. While response rates to such and other therapies are not trivial,[24-26] a favorable impact on survival or prevention of BT is uncertain and has not been shown in previously published controlled studies.[24,27-30] Similarly, other studies have consistently failed to demonstrate a reduction in mutational allele burden with CMML-directed treatment, suggesting that these therapies primarily exert epigenetic modulation rather than targeting the underlying clonal architecture of CMML.[8,9] At present, HMA are widely used as palliative therapy in CMML with overall hematologic response rates ranging from 30 to 40% and median post-treatment survival time from 20 to 36 months.[25,26,31-37] In an often quoted DACOTA randomized clinical trial comparing HU (N=86) to DAC (N=84), overall responses were 35% and 63%, respectively, median OS 18.4 and 21.9 months, median event-free survival 10.3 and 12.1 months, and 2-year BT rates 38.4% and 60.7%.[29] The current retrospective study included cohorts treated with HU or HMA, as first-line cytotoxic drugs, as well as a spectrum of other cytotoxic and non-cytotoxic drugs. The study included a relatively large number of patients with CMML (N=457) and did not show any evidence of impact on OS from any of the drugs utilized, including HMA and HU. These observations are consistent with the results from the aforementioned randomized clinical trials. What is different is the lack of impact on BT from either HMA or any other treatment strategy, as was previously suggested

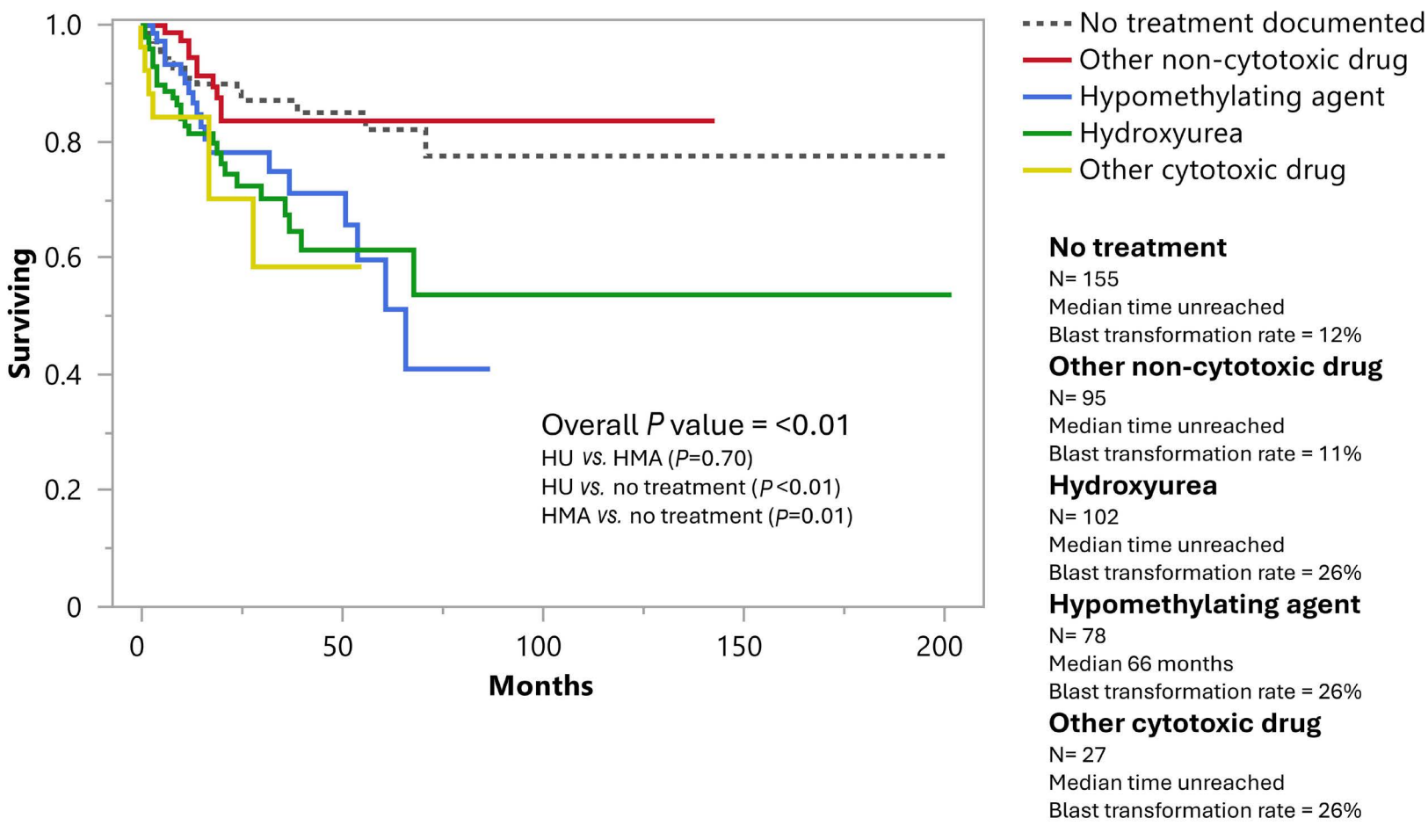

Figure 2. Blast transformation-free survival comparison among all treatment groups in 457 patients with chronic myelomonocytic leukemia. Kaplan-Meier survival curves are shown. A higher blast transformation-free survival (BTFS) is seen in patients treated with non-cytotoxic *versus* cytotoxic drugs, with the latter exhibiting a higher blast-transformation rate. HMA: hypomethylating agent; HU: hydroxyurea.

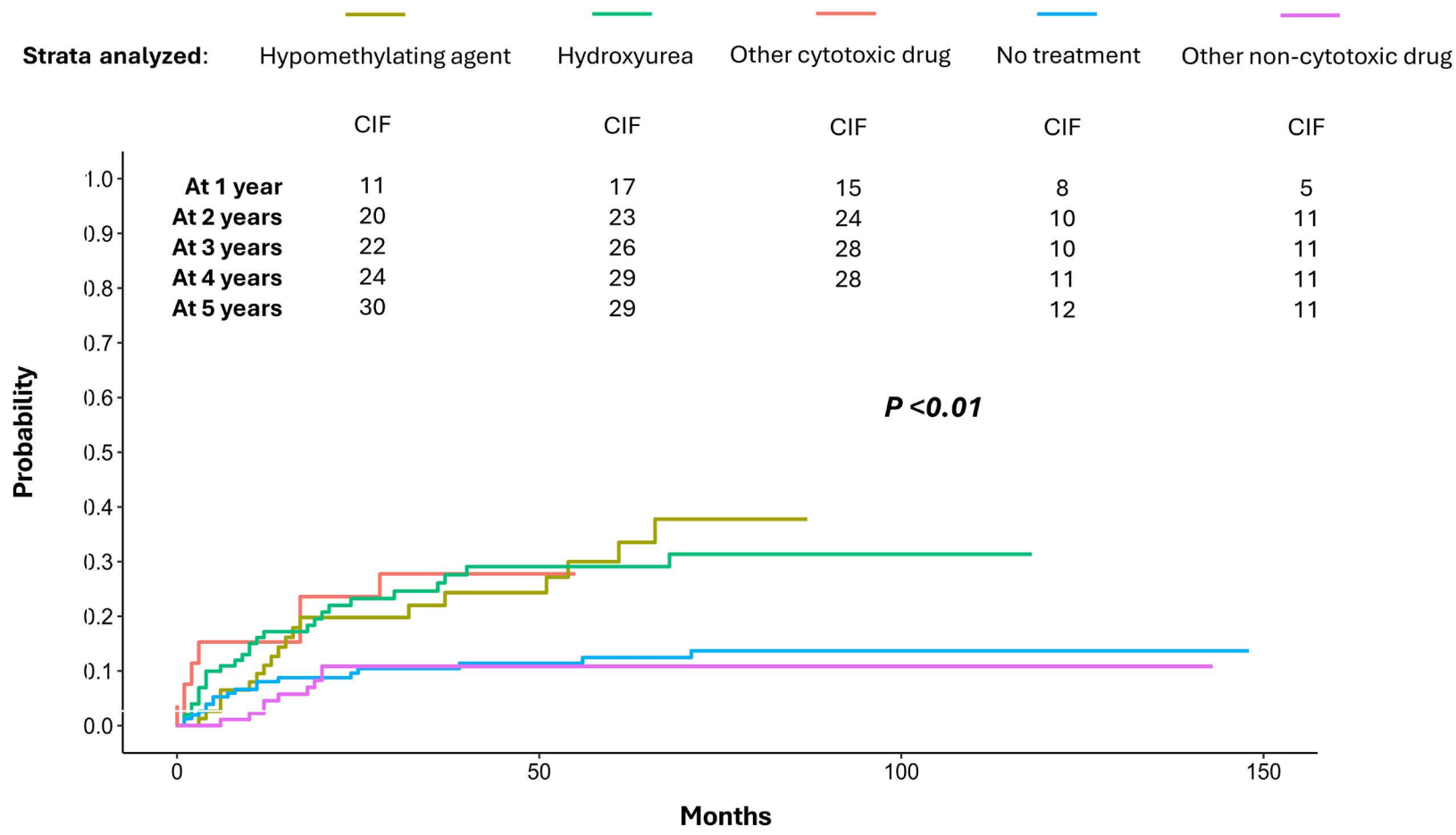

Figure 3. Cumulative incidence analysis of blast transformation in 457 patients, stratified according to their treatment groups. Death is treated as a competing risk, and cumulative incidence function (CIF) curves are presented. A higher CIF of blast transformation (BT) is seen in patients treated with non-cytotoxic *versus* cytotoxic drugs.

by the DACOTA trial.[29] Instead, the results from the current study suggest an increased incidence of BT in patients receiving cytotoxic therapy, even after accounting for other risk factors for BT. We suspect the underlying biology of patients requiring cytotoxic drug therapy rather than the effect of the drugs themselves to be the explanation for this particular observation. Our observations regarding the possible advantage of HMA over HU for treatment of leukocytosis, anemia or thrombocytopenia are also in line with those from the DACOTA trial.[7] Reassessment of response rates to DAC or AZA under revised criteria that were designed to capture improvements in both MDS and MPN features of CMML showed 86% concordance but complete remission rates were even lower at 13% (*vs*. 20% with previous criteria) because of persistent monocytosis or splenomegaly; median response durations were 22.3 months with revised criteria and 13 months with the original criteria.[38] Regardless, improvement in the MPN features did not necessarily translate into long-term survival advantage, despite the expected fact that short-term survival was longer in responders.[38]

Taken together, observations from the current and other previously published studies underscore the limited survival impact of conventional therapy in CMML and the need to promptly refer patients to be evaluated for ASCT. Our observations regarding superior survival in patients receiving ASCT has also been noted by others[39] and are currently under study by our group in a much larger study cohort of CMML patients that have undergone ASCT. The addition of venetoclax to HMA therapy in high-risk CMML might increase response rates and thus facilitate transition to ASCT.[40-42] In contrast to the experience with ASCT, the results from recent clinical trials using investigational new drugs for CMML, including tipifarnib (farnesyltransferase inhibitor), tagraxofusp (CD-123 targeted IL-3 fused to diphtheria toxin), and lenzilumab (recombinant anti-GM-CSF monoclonal antibody) have been disappointing.[43] On the other hand, non-cytotoxic treatment strategies targeting CMML-related autoimmune / inflammatory and extramedullary disease features,[44,45] constitutional symptoms / splenomegaly, thrombocytopenia, and anemia have been partially successful with corticosteroids,[5,15,46] ruxolitinib,[47] eltrombopag,[48] and ESA,[5] respectively. We acknowledge the limitations of the current study that mostly arise from its retrospective design; these include selection bias and an inadequate number of informative cases to allow a correct assessment of certain endpoints. Nevertheless, our observations highlight the dire need for research and drug development in CMML.

Disclosures

No conflicts of interest to disclose.

Contributions

MY and AT performed the data analysis and wrote the paper; MY, PF, MA, FA, SF, AKAA and CMC participated in data collection; AT, MMP, AP, AAM and NG were involved with patient

care; KKR and RH provided hemato-pathology expertise; TL provided molecular laboratory expertise. All authors reviewed and approved the final manuscript for publication.

Data-sharing statement

All requests should be made to the corresponding author.

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