original reports

Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network

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abstract

PURPOSE Hydroxyurea (HY) is a reference treatment of advanced myeloproliferative neoplasms. We conducted a randomized phase III trial comparing decitabine (DAC) and HY in advanced myeloproliferative chronic myelomonocytic leukemias (CMML).

PATIENTS AND METHODS Newly diagnosed myeloproliferative CMML patients with advanced disease were randomly assigned 1:1 to intravenous DAC (20 mg/m^2/d days 1-5) or HY (1-4 g/d) in 28-day cycles. The primary end point was event-free survival (EFS), events being death and acute myelomonocytic leukemia (AML) transformation or progression.

RESULTS One-hundred seventy patients received DAC (n = 84) or HY (n = 86). Median age was 72 and 74 years, and median WBC count 32.5×10^9/L and 31.2×10^9/L in the DAC and HY arms, respectively. Thirty-three percent of DAC and 31% of HY patients had CMML-2. Patients received a median of five DAC and six HY cycles. With a median follow-up of 17.5 months, median EFS was 12.1 months in the DAC arm and 10.3 months in the HY arm (hazard ratio [HR], 0.83; 95% CI, 0.59 to 1.16; $P = .27$). There was no significant interaction between treatment effect and blast or platelet count, anemia, CMML Prognostic Scoring System, Groupe Francophone des Myelodysplasies, or CMML Prognostic Scoring System–mol risk. Fifty-three (63%) DAC patients achieved a response compared with 30 (35%) HY patients ($P = .0004$). Median duration of response was similar in both arms (DAC, 16.3 months; HY, 17.4 months; $P = .90$). Median overall survival was 18.4 months in the DAC arm and 21.9 months in the HY arm ($P = .67$). Compared with HY, DAC significantly reduced the risk of CMML progression or transformation to acute myelomonocytic leukemia (cause-specific HR, 0.62; 95% CI, 0.41 to 0.94; $P = .005$) at the expense of death without progression or transformation (cause-specific HR, 1.55; 95% CI, 0.82 to 2.9; $P = .04$).

CONCLUSION Compared with HY, frontline treatment with DAC did not improve EFS in patients with advanced myeloproliferative CMML (ClinicalTrials.gov identifier: NCT02214407).

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INTRODUCTION

Chronic myelomonocytic leukemias (CMML) are rare myeloid neoplasms with myelodysplastic and myeloproliferative features.[1] The myeloproliferative subset of CMML (MP-CMML), defined by a WBC count $\geq 13 \times 10^9$/L,[2,3] represents 40%-50% of patients with CMML and is endowed with poor prognosis.[4]

In MP-CMML patients ineligible for allogeneic transplantation (HSCT), cytoreduction remains a standard of care. In a previous randomized clinical trial, hydroxyurea (HY) provided superior response rates and survival versus oral etoposide in MP-CMML with protocol-defined criteria for advanced disease, including blast excess, abnormal karyotype, significant cytopenias, or splenomegaly.[5] Response criteria in this trial accounted for improvement of both myelodysplastic and myeloproliferative traits of CMML, predating the more recent international myelodysplastic syndrome/myeloproliferative neoplasm response criteria.[6]

CONTEXT

Key Objective

To our knowledge, we conducted the first randomized study dedicated to chronic myelomonocytic leukemia to determine whether the hypomethylating agent decitabine (DAC) improves event-free survival in proliferative patients compared with standard cytoreduction by hydroxyurea (HY).

Knowledge Generated

There was no difference in event-free survival or overall survival between patients with advanced proliferative chronic myelomonocytic leukemia (CMML) treated with DAC compared with HY. The highest response rate of DAC was offset by increased toxicity notably of infectious or cardiovascular origin.

Relevance (C.F. Craddock)

HY remains a valid treatment option in proliferative CMML. Prospective randomized trials of novel treatment strategies in proliferative CMML are required.*

*Relevance section written by JCO Associate Editor Charles F. Craddock, MD.

Hypomethylating agents (HMAs) have also been explored in MP-CMML in retrospective[7-9] and nonrandomized prospective studies.[10-12] Durable responses were obtained with decitabine (DAC), including in a phase II trial enrolling MP-CMML patients with advanced disease as defined by the randomized HY trial.[10,12]

The DACOTA trial was designed by the European Myelodysplastic Syndromes Cooperative Group to compare HY and DAC as frontline strategies for MP-CMML with advanced disease.

PATIENTS AND METHODS

Study Design

The DACOTA trial was a phase III, two-arm, randomized, stratified, multicenter, open-label study. Patients from 47 centers in France, Germany, and Italy were enrolled between October 2014 and September 2019 and randomly assigned 1:1 to receive DAC (with or without HY during the first three cycles, DAC arm) or HY only (HY arm). Random assignment was stratified by country, WHO 2010 category,[2] and severe anemia (hemoglobin [Hb] < 8 g/dL or RBC concentrate transfusion dependence [≥ 4 RBC concentrates for a Hb level < 9 g/dL since diagnosis]).

Patients in the HY arm started oral HY at 1 g once daily, with dose adjustments up to 4 g once daily to maintain a WBC count between 5 and 10×10^9/L. HY was discontinued in cases of grade 4 thrombocytopenia or neutropenia and reintroduced at a lower dose after recovery to grade ≤ 3. Patients in the DAC arm received DAC 20 mg/m² intravenously once daily on days 1-5 of each cycle. HY could be added during the first three cycles if WBC count was $> 30 \times 10^9$/L.

Patients received study treatment in 28-day cycles until reaching a protocol-defined event, or until unacceptable toxicity defined as a treatment-emergent nonhematologic grade 3-4 adverse events (AEs) according to Common Terminology Criteria for Adverse Events 4.0 criteria not recovering to grade ≤ 2 with adequate dosing delay, or a grade 4 hematologic toxicity not resolving to grade ≤ 3 after 4-week delay.

Concomitant use of erythropoiesis-stimulating agents, granulocyte colony-stimulating factor, or thrombopoietin analogs was not allowed. Patients with prolonged neutropenia could receive antimicrobial and antifungal prophylaxis at the investigator's discretion.

Eligibility Criteria

Previously untreated patients (except erythropoiesis-stimulating agent or < 6-week HY) ≥ 18 years with WHO 2010–defined CMML,[2] Eastern Cooperative Oncology Group performance status ≤ 2, adequate organ function, and a WBC count $\geq 13 \times 10^9$/L on two CBCs ≥ 2 weeks apart (before HY onset) were eligible if presenting with advanced disease defined as previously,[5,10] by either a documented extramedullary disease (except splenomegaly) or ≥ 2 criteria among bone marrow blasts ≥ 5%, clonal cytogenetic abnormality (other than isolated -Y), Hb level < 10 g/dL, absolute neutrophil count $> 16 \times 10^9$/L (outside of an infection), platelet count $< 100 \times 10^9$/L, and splenomegaly > 5 cm below costal margin. Patients eligible for HSCT at screening were excluded.

End Points and Assessments

The primary end point was event-free survival (EFS). Events included death from any cause, transformation to WHO-defined acute myelomonocytic leukemia (AML) at any time, progression defined either after ≥ 6 cycles as a doubling of bone marrow blasts from baseline or from best response to > 10%, and worsening of cytopenias lasting for > 4 weeks; or after ≥ 3 cycles as ≥ 50% increase in spleen size (determined by an imaging technique), doubling in WBC from baseline or best response, or occurrence of a

previously undiagnosed extramedullary disease despite maximal protocol-defined HY or DAC dosing in the absence of concomitant infection.

Secondary end points were overall survival (OS), cumulative incidence of AML, overall response rate, and complete response (CR) rate after three and six cycles according to IWG 2006 criteria modified for CMML as per Wattel et al[5,10] and response duration. Details on response assessment and criteria are provided in the Data Supplement.

Statistical Analyses

Considering a 24-month accrual, a minimum follow-up time of 12 months, and a drop-out of 5%, a sample size of 168 patients (84 in each arm) was necessary to detect a ≥ 35% improvement in the 12-month EFS rate from 50% to 68% by using the log-rank test in one of the arms (corresponding to a hazard ratio [HR] of 0.56) with an alpha risk of .05 and a power of 80% (two-sided test).

All analyses including response assessment were performed on the intent-to-treat (ITT) principle. Baseline characteristics of the two treatment groups were summarized using median (interquartile range [IQR]) or percentages, with no statistical tests as recommended. Follow-up data on survival, AML transformation, and subsequent therapy (including HMAs in the HY arm) were collected beyond study exit until the data cutoff date of September 13, 2021. Overall and complete response rates were compared across randomized groups using the Fisher exact test; missing outcomes were considered as failures. Censored data were analyzed using the Kaplan-Meier estimator and the log-rank test, unless a competing setting where cumulative incidence of progression or AML transformation was estimated, with comparison across baseline groups on the basis of the Gray test. Prognostic analyses of EFS and OS used Cox proportional hazards models, while those of progression or AML transformation used cause-specific Cox models. Model assumptions were checked using the Grambsch and Therneau test for proportional hazards and a generalized additive model with regression splines for the log-linearity assumption. Qualitative and quantitative interactions between treatment effect and subgroups were tested with the Gail and Simon interaction test. All statistical analyses were performed with R software version 3.0.2. Two-sided P values of .05 or less denoted statistical significance.

Study Oversight

The study Protocol (online only) and amendments were approved by the ethics committee of each participating institution. The amended study protocol (including safety assessment procedures) is available as the Data Supplement. All patients provided written consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the guidelines for Good Clinical Practice of the International Conference on Harmonisation, European directives, and national legislations on clinical trials. An independent data and safety monitoring board oversaw the trial, assessing safety and efficacy, and recommended completion of accrual after an unplanned interim analysis of the first 84 randomly assigned patients, triggered by the slow accrual in the study. The study is registered on EudraCT (2014-000200-10) and ClinicalTrials.gov (identifier: NCT02214407).

RESULTS

Study Population

The ITT population comprised 170 patients randomly assigned to DAC (n = 84) or HY (n = 86) arms (Fig 1). Median age was 72 years (IQR, 66-77 years) and 74 years (IQR, 69-79 years) in the DAC and HY arms, respectively. Twenty-eight (33%) and 27 (31%) patients had CMML-2 per WHO 2010 classification, and median WBC count was 32.5×10^9/L (IQR, 21.3-55.3×10^9/L) and 31.2×10^9/L (IQR, 20.4-46.0×10^9/L) in the DAC and HY arms, respectively. Thirty-four (40%) and 35 (41%) patients randomly assigned to the DAC and HY arms had been exposed to HY before random assignment, respectively (Table 1).

Centralized gene mutation analyses were available in 160 (94%) patients (Data Supplement). Groupe Francophone des Myelodysplasies (GFM) risk was high in 38 (49%) DAC patients and 46 (56%) HY patients (Table 1).

Patients received a median of five (IQR, 3-13, range 0-50) cycles in the DAC arm and six (IQR 3-16, range 0-72) cycles in the HY arm. Thirty (36%), five (6%), and three (4%) patients in the DAC arm were still receiving HY at the onset of cycle 1, 2, and 3, respectively. At data cutoff, eight DAC and 13 HY patients remained on treatment. Forty-one DAC and 46 HY patients received at least six treatment cycles (Fig 1).

Primary Outcome

With a median follow-up of 17.5 months (DAC arm 16.9 months, HY arm 17.8 months), 135 patients developed at least one event (68 and 67 in the DAC and HY arms, respectively), the first event being progression of myeloproliferation in 30, blast count progression in 39, AML transformation in 20, and death in 46. Median EFS was 12.1 months (95% CI, 8.9 to 19.9) in the DAC arm, compared with 10.3 months (95% CI, 6.7 to 17.9) in the HY arm. Two-year EFS estimates were 34% (95% CI, 25 to 46) in the DAC arm and 22% (95% CI, 14 to 34) in the HY arm (HY arm as reference, HR, 0.83; 95% CI, 0.59 to 1.16; P = .27; Fig 2A). There was no evidence of interaction between treatment and blast count ≥ 10%, platelet count $< 100 \times 10^9$/L, severe anemia, int-2/high CMML Prognostic Scoring System (CPSS) risk, high GFM, or CPSS-mol risk (Fig 2B).

Secondary Outcomes

A total of 47 (56%) patients in the DAC arm achieved a response at three cycles compared with 27 (31%) in the HY arm (relative risk [RR], 0.56; 95% CI, 0.39 to 0.81;
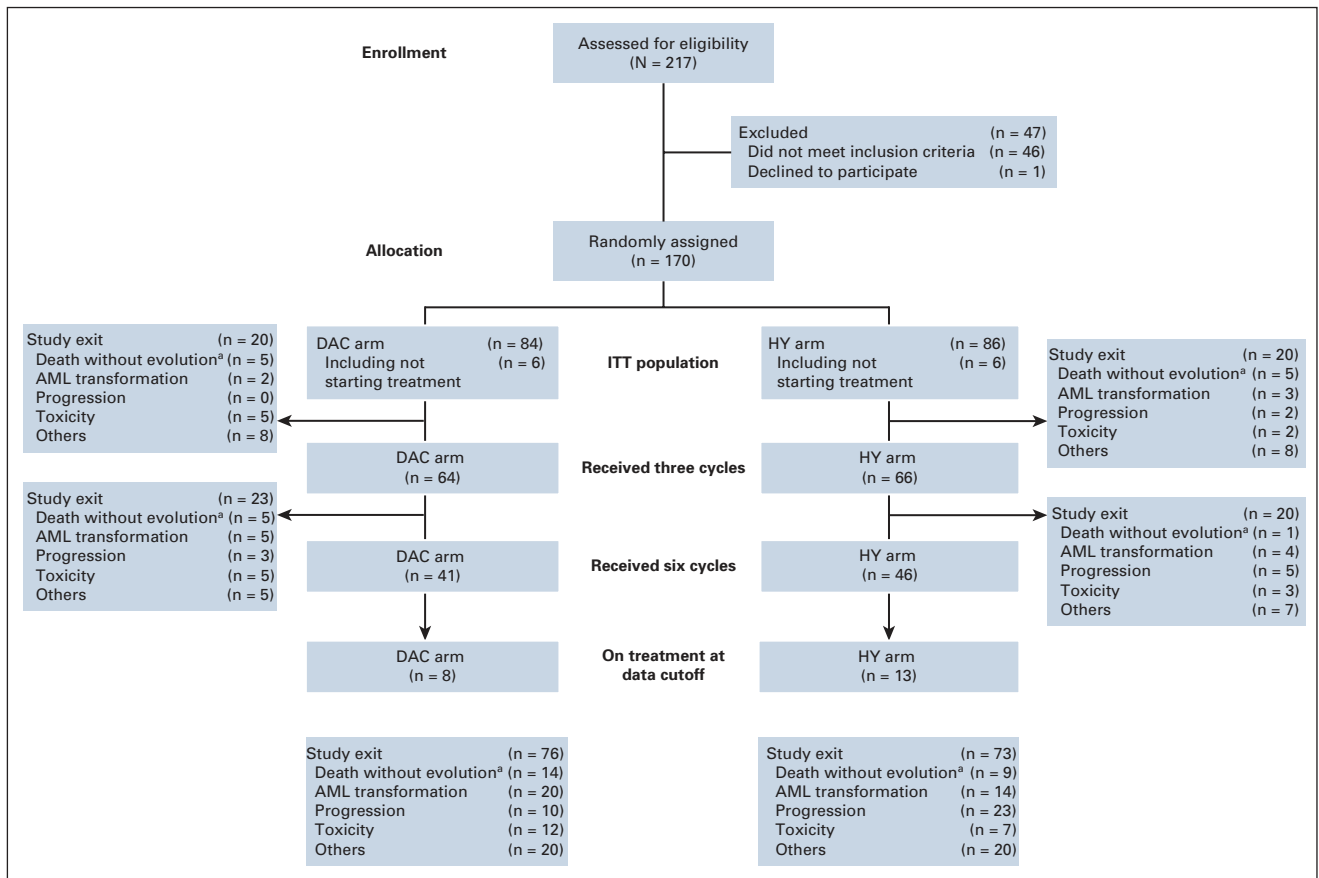
FIG 1. CONSORT diagram of the DACOTA trial. [a]Evolution includes protocol-defined progression and AML transformation. AML, acute myelomonocytic leukemia; DAC, decitabine; HY, hydroxyurea; ITT, intent-to-treat.

$P = .002$). Responses in the DAC arm included seven CR, 22 marrow CR (mCR) with hematologic improvement (HI), three mCR without HI, and 15 stable diseases (SD) with HI. Responses in the HY arm were 0 CR, five mCR with HI, three mCR without HI, and 19 SD with HI. After six cycles, there were 27 (32%) responders in the DAC arm (CR [n = 6], mCR with HI [n = 9], SD with HI [n = 12]) versus 15 (17%) in the HY arm (CR [n = 2], mCR with HI [n = 2], mCR without HI [n = 2], SD with HI [n = 9]; RR, 0.54; 95% CI, 0.31 to 0.95; $P = .033$). Overall, 53 (63%) patients in the DAC arm responded at any time compared with 30 (35%) in the HY arm (RR = 0.55; 95% CI, 0.40 to 0.77; $P = .0004$). CRs were also more frequent in the DAC arm (n = 10, 12%) compared with HY arm (n = 2, 2%) (RR, 0.19; 95% CI, 0.04 to 0.86; $P = .017$). Of 52 patients with abnormal cytogenetics at screening, 21 were evaluated for cytogenetic response, two of whom (DAC [n = 1], HY [n = 1]) achieved complete cytogenetic response. Targeted sequencing of monocytes after six cycles of DAC (n = 9) and HY (n = 13) revealed an erosion of secondary mutations in patients achieving CR (Data Supplement).

Median duration of response was 16.3 months (95% CI, 7.2 to 26.8) in the DAC arm and 17.4 months (95% CI, 9.8

to 26.9) in the HY arm ($P = .90$; Table 2). Beyond the first event, an additional 47 patients transformed to AML, and 78 died. Median OS was 18.4 months (95% CI, 13.6 to 30.4) in the DAC arm compared with 21.9 months (95% CI, 17.7 to 27.6) in the HY arm, with 2-year OS estimates of 44% (95% CI, 35 to 57) and 44% (95% CI, 34 to 57), respectively (HY arm as reference, $P = .67$, HR, 1.08; 95% CI, 0.76 to 1.54; Fig 2C). There was no evidence of heterogeneity in treatment effect on OS (Fig 2D). The 2-year cumulative incidence of progression or AML transformation was 38.4% (95% CI, 27.9 to 48.8) in the DAC arm versus 60.7% (95% CI, 48.5 to 70.9) in the HY arm (HY arm as reference, cause-specific HR, 0.62; 95% CI, 0.41 to 0.94; $P = .005$). Conversely, the 2-year cumulative incidence of death without progression or transformation was 27.5% (95% CI, 18.4 to 37.4) in the DAC arm versus 17.4% (95% CI, 9.7 to 27.0) in the HY arm (cause-specific HR, 1.55; 95% CI, 0.82 to 2.9; $P = .04$, Fig 3). Concomitant HY administration in the DAC arm during cycle 1 had no impact on the cumulative incidence of progression or AML transformation ($P = .52$) or death without progression/transformation ($P = .42$). After treatment discontinuation, 35 of the 59 (59%) HY patients alive at study exit went on to receive an HMA (azacitidine n = 20, DAC n = 15).

TABLE 1. Baseline Characteristics of the ITT Population

Baseline Characteristic	DAC (n = 84)	HY (n = 86)
Age, years, median (IQR)	72 (67-77)	74 (69-79)
Male sex, No. (%)	56 (67)	61 (71)
ECOG, No. (%)		
0	32 (38)	36 (42)
1	44 (52)	40 (47)
2	8 (10)	9 (11)
WHO 2010, No. (%)		
CMML-1	56 (67)	59 (69)
CMML-2	28 (33)	27 (31)
Cytogenetic risk, No. (%)		
Low	62 (74)	56 (65)
Intermediate	7 (8)	12 (14)
High	14 (17)	16 (19)
Not available	1 (1)	2 (2)
Median WBC count, ×10⁹/L (IQR)	32.5 (21.3-55.3)	31.2 (20.4-46.0)
Median neutrophil count, ×10⁹/L (IQR)	17.5 (9.6-26.8)	14.7 (8.2-22.8)
Severe anemia, No. (%)[a]	19 (23)	21 (24)
Splenomegaly, No. (%)[b]	34 (40)	35 (41)
CPSS risk, No. (%)		
Low	0 (0)	1 (1)
Intermediate-1	35 (42)	31 (37)
Intermediate-2	44 (52)	46 (53)
High	4 (5)	6 (7)
Not available	1 (1)	2 (2)
GFM risk, No. (%)[c]		
Low	5 (6)	4 (5)
Intermediate	35 (45)	32 (39)
High	38 (49)	46 (56)
CPSS-mol risk, No. (%)[c]		
Low	0 (0)	0 (0)
Intermediate-1	5 (7)	6 (7)
Intermediate-2	40 (51)	39 (48)
High	32 (41)	36 (44)
Not available	1 (1)	1 (1)
Past HY exposure, No. (%)	34 (40)	35 (41)
Days past HY, median (IQR)	27 (20-42)	31 (17-44)

Abbreviations: CMML, chronic myelomonocytic leukemias; CPPS, CMML Prognostic Scoring System; DAC, decitabine; ECOG, Eastern Cooperative Oncology Group; GFM, Groupe Francophone des Myelodysplasies; Hb, hemoglobin; HY, hydroxyurea; IQR, interquartile range; ITT, intent-to-treat.

[a]Baseline Hb level < 8 g/dL or RBC transfusion dependence (at least four RBC concentrates for a Hb level < 9 g/dL since diagnosis).

[b]Palpable spleen and craniocaudal length > 13 cm by ultrasound or computed tomography scan.

[c]N = 160 with centralized genetics.

Censoring patients from the HY arm at HMA onset, the HR for death in the DAC arm (considering HY as reference) was 1.41 (95% CI, 0.92 to 2.16; $P = .11$). Fifteen patients received HSCT (10 in the DAC arm and five in the HY arm), including eight after progression or AML transformation.

Safety

AEs and hospitalization rates in the ITT population are reported in Table 3 and the Data Supplement. Fifty DAC (60%) and 34 (40%) HY patients required hospitalization ($P = .01$). Fifty-eight (69%) patients in the DAC arm and 45 (52%) patients in the HY arm had at least one infection (all grades) during study duration ($P = .03$). Grade ≥ 3 infections occurred across all cycles in 28 (33%) and 16 (18%) DAC and HY patients, respectively ($P = .04$). A similar nonsignificant trend was noted over the first three treatment cycles (Table 3). Details on the 196 infectious episodes (DAC n = 109, HY n = 87) are reported in the Data Supplement. Across all cycles, antibacterial prophylaxis was administered in 27 (32%) DAC and 9 (10%) HY patients, and antifungal prophylaxis in 16 (19%) DAC and three (3%) HY patients (Data Supplement). Thirty-six (43%) patients in the DAC arm and 32 (37%) in the HY arm experienced at least one bleeding episode (all grades, $P = .53$). There was no imbalance in the proportion of patients experiencing grade ≥ 3 hemorrhage ($P = 1$). Grade ≥ 3 cardiovascular AEs occurred in 16 (20%) DAC and six (7%) HY patients ($P = .02$; Data Supplement). Twenty-three patients died on study without previous progression or transformation (DAC n = 14, HY n = 9). Causes of all deaths occurring on study or during follow-up are reported in the Data Supplement.

DISCUSSION

In this randomized, stratified, open-label phase III trial involving MP-CMML patients with advanced disease, DAC at the conventional 5-day intravenous regimen resulted in better response rates but only a nominal 17% reduction of the RR of death, transformation to AML, or disease progression (ie, EFS) compared with HY, not meeting the primary end point of the study.

To the best of our knowledge, this academic study represents the first randomized trial dedicated to this rare patient population over the past two decades.[13] MP-CMML, defined using the WHO cutoff of WBC count ≥ 13 × 10⁹/L, remains a CMML subset with poorer prognosis.[4] The study selected patients with advanced disease on the basis of criteria used in two previous studies, including a randomized trial of HY versus oral etoposide,[5] and a nonrandomized phase II study of DAC.[10] Since the design of the DACOTA trial, several independently validated prognostic scores have been proposed in CMML, on the basis of hematologic and cytogenetic data only such as CPSS[14] or
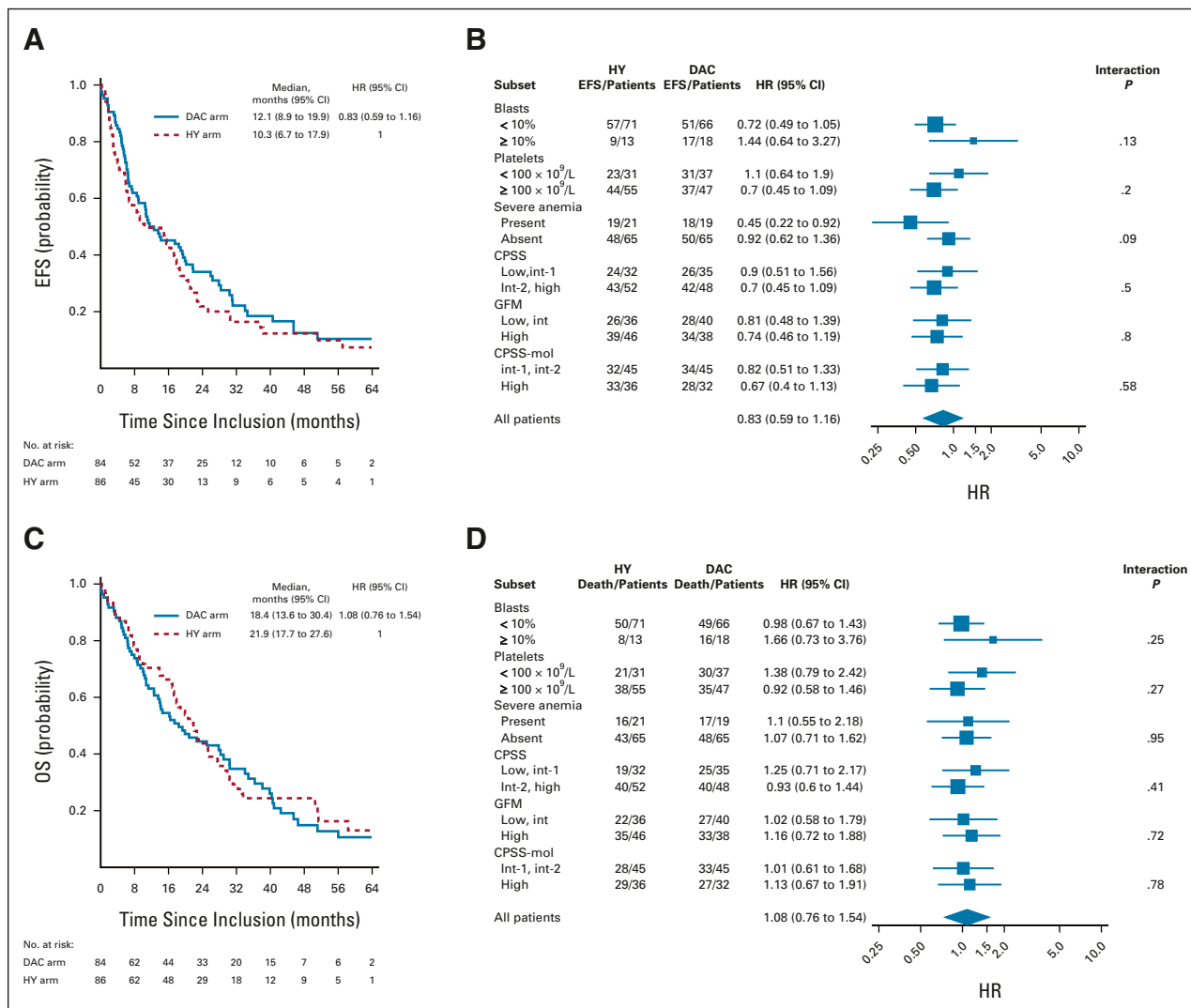
FIG 2. (A) Kaplan-Meier estimation and (B) subgroup analysis of EFS in the ITT population. (C) Kaplan-Meier estimation and (D) subgroup analysis of OS in the ITT population. HRs are provided considering the HY arm as reference. CPPS, Chronic Myelomonocytic Leukemia Prognostic Scoring System; DAC, decitabine; EFS, event-free survival; GFM, Groupe Francophone des Myelodysplasies; HR, hazard ratio; HY, hydroxyurea; ITT, intent-to-treat; OS, overall survival; Pts, patients.

including recurrent somatic mutations.[15-17] Although 57% DAC and 60% HY patients were considered at higher (intermediate-2 or high) risk on the basis of CPSS, 92% of patients in each arm were reclassified as higher risk when incorporating recurrent somatic mutations according to the molecular CPSS, confirming that our study accrued a high-risk patient population. Except for a trend toward older age in the HY arm (median age 74 years v 72 years in the DAC arm), there was no imbalance between the two arms. This was also true with respect to mutational profiles.

Our findings contrast with a previous retrospective report suggesting a survival benefit with HMAs versus HY in pro-liferative CMML, stressing the need for prospective, ran-domized studies including in rare myeloid neoplasms.[18] Several nonmutually exclusive hypotheses could account for the comparable outcome of patients randomly assigned to

the HY arm and DAC arm. Concomitant, but not sequential, treatment with HY and DAC may hinder DNA demethylation.[19] Although 40% of DAC patients had previously been exposed to HY, only 7% were still receiving HY at the start of the second cycle of DAC. On the basis of previous nonrandomized trials and retrospective cohorts,[8-12,18] HMAs are considered as valid treatment options in proliferative CMML, except in regions such as the European Union where their label is restricted to the myelodysplastic CMML subset,[20] or to patients with AML transformation.[21] Many (59%) patients in the HY arm went on to receive HMAs at study exit. Although censoring patients from the HY arm at the onset of HMA beyond study exit did not uncover a significant difference in OS between the two arms (P = .11), this may have blurred a potential OS advantage of frontline DAC. The overall response rate of 63% with DAC was clearly superior to that seen with HY (35%), although duration

TABLE 2. Response per Protocol in the ITT Population

Response	At Three Cycles (ITT)			At Six Cycles (ITT)			Best Response (ITT)		
	DAC	HY	*P*	DAC	HY	*P*	DAC	HY	*P*
CR, No. (%)	7 (8)	0 (0)	.006	6 (7)	2 (2)	.17	10 (12)	2 (2)	.017
mCR with HI, No. (%)	22 (26)	5 (6)		9 (11)	2 (2)		22 (26)	4 (5)	
mCR without HI, No. (%)	3 (4)	3 (3)		0 (0)	2 (2)		3 (4)	4 (5)	
SD with HI, No. (%)	15 (18)	19 (22)		12 (14)	9 (11)		18 (21)	20 (23)	
SD without HI, No. (%)	2 (3)	14 (16)		0 (0)	9 (11)		1 (1)	13 (15)	
PD, No. (%)	7 (8)	9 (10)		6 (7)	12 (14)		4 (5)	8 (9)	
Not evaluable,[a] No. (%)	28 (33)	36 (43)		51 (61)	50 (58)		26 (31)	35 (41)	
ORR, No. (%)	47 (56)	27 (31)	.002	27 (32)	15 (17)	.03	53 (63)	30 (35)	.0004
ORR excluding SD + HI-Pro, No. (%)	33 (39)	13 (15)	.0004	22 (26)	7 (8)	.002	40 (48)	16 (19)	.00008
DOR, months, median (95% CI)							16.3 (7.2 to 26.8)	17.4 (9.8 to 26.9)	.90

Abbreviations: CR, complete response; DAC, decitabine; DOR, duration of response; HI, hematologic improvement; HI-Pro, hematologic improvement of proliferation; HY, hydroxyurea; ITT, intent-to-treat; mCR marrow CR; ORR, overall response rate; PD, progressive disease; SD, stable disease.

[a]Patients not evaluable because of study exit before the completion of three (n = 40) or six (n = 83) cycles or those without bone marrow assessment at the three-cycle (n = 24) and six-cycle (n = 18) evaluations were considered as nonresponders.

of response was similar in both arms. This suggests that DAC remains a relevant bridge to transplantation, although transplant-eligible patients were not accrued to this study. Our study was designed before the release of myelodysplastic syndrome/myeloproliferative neoplasms international response criteria, which should be used in future studies.[6] The superior response rate provided by DAC held true in an exploratory analysis considering patients with stable marrow disease and cytopenias but with improvement in WBC count or spleen size (15% and 16% such patients in the DAC and HY arms, respectively) as nonresponders. A retrospective analysis of HMA-treated CMML patients failed to identify a clear survival benefit conferred by such improvement of myeloproliferative features.[22] Assessment of patient-reported outcomes will be an invaluable addition to future CMML trials.[23] A competing risk analysis confirmed that DAC provides a significant 38% reduction in the specific risk of CMML progression or transformation to AML. The same analysis revealed an unexpected 55% increase in the specific risk of death without prior progression or transformation. This finding warrants cautious interpretation since those deaths partially occurred after study exit. The median of five cycles received in
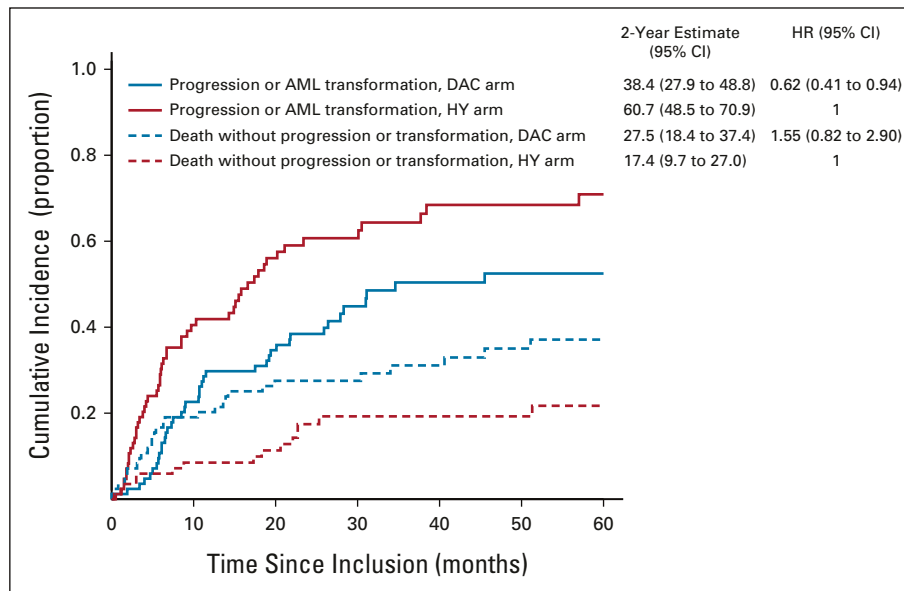

FIG 3. Cumulative incidence of progression or AML transformation (solid lines) and death without progression or AML transformation (dashed lines) considered as competing risks, in the ITT population. AML, acute myelomonocytic leukemia; DAC, decitabine; HR, hazard ratio; HY, hydroxyurea; ITT, intent-to-treat.

TABLE 3. Adverse Events and Hospitalization Rates in the ITT Population

	All Cycles			First Three Cycles		
Patients With ≥ 1 AE	DAC, No. (%)	HY, No. (%)	P	DAC, No. (%)	HY, No. (%)	P
Hospitalization	50 (60)	34 (40)	.01	28	18	.08
Infections	58 (69)	45 (52)	.03	35 (41)	25 (29)	.11
Grade 1-2	30 (36)	29 (34)		20 (24)	18 (21)	
Grade 3	15 (18)	8 (9)	.04	7 (8)	5 (6)	.07
Grade 4	1 (1)	1 (1)		1 (1)	0 (0)	
Grade 5	12 (14)	7 (8)		7 (8)	2 (2)	
Hemorrhages	36 (43)	32 (37)	.53	27 (32)	27 (31)	1
Grade 1-2	30 (36)	27 (31)		23 (27)	23 (27)	
Grade 3	3 (4)	3 (4)	.76	2 (2)	2 (2)	1
Grade 4	0 (0)	1 (1)		0 (0)	1 (1)	
Grade 5	3 (4)	1 (1)		2 (2)	1 (1)	
Cardiovascular	26 (31)	12 (14)	.01	12 (14)	8 (9)	.35
Grade 1-2	10 (12)	6 (7)		6 (7)	3 (3)	
Grade 3	10 (12)	4 (5)	.02	4 (5)	4 (5)	.76
Grade 4	3 (4)	1 (1)		2 (2)	1 (1)	
Grade 5	3 (4)	1 (1)		0 (0)	0 (0)	
Pulmonary	20 (24)	17 (20)	.58	13 (15)	9 (10)	.37
Grade 1-2	14 (17)	9 (10)		9 (11)	5 (6)	
Grade 3	4 (5)	4 (5)	.78	3 (3)	2 (2)	1
Grade 4	2 (2)	3 (4)		1 (1)	2 (2)	
Grade 5	0 (0)	1 (1)		0 (0)	0 (0)	

NOTE. Other categories of AE with grade ≥ 3 events occurring in < 5% (eight patients) and changes in liver and renal function tests are reported in the Data Supplement. P values of Fisher tests for between-arm differences on all AEs and on grade ≥ 3 AEs.

Abbreviations: AE, adverse event; DAC, decitabine; HY, hydroxyurea; ITT, intent-to-treat.

the DAC arm is lower than previous trials reporting a median 6-10 DAC cycles.[10,12] A greater proportion of DAC patients experienced grade ≥ 3 infections and cardiovascular AEs compared with HY patients. The study population was old and thus vulnerable to infections. Further studies accounting for comorbidities will be required to determine whether this increased risk was associated with more severe myelosuppression with DAC. On the basis of existing evidence, it is unclear whether systematic antimicrobial prophylaxis or reduced DAC regimens would have improved safety.[24,25] Cases of DAC-related cardiomyopathy have been reported,[26,27] and 8 of 10 heart failure AEs occurred in patients with a history of cardiac disease or hypertension. Cardiovascular monitoring may thus be necessary in those patients when initiating DAC treatment. Our heterogeneity analyses including the GFM and CPSS-mol scoring systems that account for somatic mutations did not delineate a subset of patients with a clear EFS or OS benefit with DAC. Ancillary biology studies investigating methylation-based biomarkers and longitudinal cytokine profiling are ongoing.[28] Future studies will aim at translating the superior response rate noted with DAC in this study into a significant long-term survival benefit. Our results stress the need for international, randomized clinical trials in rare and heterogeneous neoplasms such as CMML.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network

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