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Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine

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ABSTRACT

Treatment of CMML remains a clinical challenge, with no drug demonstrating clear clinical benefit. Even if azacitidine is approved in the treatment of CMML, its role remains disputed. We report a cohort of 76 CMML patients (according to WHO classification) treated with azacitidine in 3 programs (French AZA compassionate program, Cleveland Clinic Foundation and H. Lee Moffitt Cancer Center). 45% had CMML2, and 55% had splenomegaly and/or WBC counts >13 G/L, which are known to be poor prognostic factors in CMML. All patients received AZA for at least one cycle, and the median number of cycles administered was 6. Thirty-three patients (43%) achieved a response according to IWG 2006 criteria, including 13 complete remissions (17%). Median survival was 29 months. Increased bone marrow blast percentage and proliferative features of the disease, including splenomegaly and high WBC counts, were significantly associated with shorter survival. By multivariate analysis, only marrow blasts >10% and palpable splenomegaly had prognostic impact on survival. Although promising, the efficacy of azacitidine in advanced CMML needs to be confirmed in a randomized prospective study.

1. Background

Chronic myelomonocytic leukemia (CMML), recognized as a myelodysplastic/myeloproliferative neoplasm according to the WHO classification [1], is characterized by the accumulation of monocytes in the blood and bone marrow, a variable proportion of immature blasts in the bone marrow (less than 20%) and by dysplastic hematopoiesis. As some patients have increased WBC counts and/or organ involvement (mainly splenomegaly and less often skin infiltration or serous effusions), it has been proposed to distinguish two subgroups of CMML based on the WBC count, a myelodysplastic type (MDS-CMML) (WBC $< 13 \times 10^9$/L) and a myeloproliferative type (MPN-CMML) (WBC $> 13 \times 10^9$/L). While these subgroups have different clinical characteristics (e.g., splenomegaly and extramedullary hematopoiesis is more commonly associated with MPN-CMML), there is no significant difference in outcome using conventional treatment [2,3].

The prognosis of CMML is variable, with an approximately 2.5-year median survival. Prognostic factors associated with survival or AML evolution include the bone marrow blast percentage, which distinguishes CMML1 from CMML2 (0–9% blast for CMML1 and 10–19% in CMML2), cytopenias, abnormal karyotype, and myeloproliferative features (including increased WBC count, presence of splenomegaly, circulating immature myeloid precursors, and extramedullary disease), attempts having been made to combine those factors in prognostic scoring systems [4]. Recently, several somatic gene mutations, including polycomb gene mutations (ASXL1 and EZH2), have been reported to negatively affect CMML outcome.

Treatment of CMML remains a clinical challenge, with no therapy having been shown to alter the natural history of the disease short of allogeneic stem cell transplant. Common approaches include hydroxyurea (HU), and VP 16 (etoposide). While treatment with the drug azacitidine prospectively yielded a survival benefit in higher-risk MDS patients, few CMML patients were included as subjects [5]. Attempts have been made to report outcomes for CMML patients treated with hypomethylating agents [6–10] though patient numbers were limited, and with heterogeneous risk factors in most series. We herein report results in the largest series of CMML patients treated with azacitidine.

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Table 1
Patient characteristics.

	N	%
Age (years)		
Median	70	–
Range	33–85	–
Sex		
Male	47	–
Female	29	–
WBC (10^9/L)		
Median	11.4	–
Range	1–122	–
WBC > 13 × 10^9/L	33/72	46
Hemoglobin (g/dL)		
Median	10	–
Range	6.3–15.2	–
Platelets (10^9/L)		
Median	59	–
Range	9–1214	–
Splenomegaly	23/72	
Cytogenetics		
Normal	38	55
5 ou 7 abn	10	15
Others	21	30
% BM blasts		
Median	8	–
Range	0–19	–
IPSS in patients with WBC < 13 G/L		
Low and Int-1	17	46
Int-2 and High	20	54
Disease duration		
<6 months	30	42
6–12 months	10	14
>12 months	31	44
Prior therapy		
None	40	54
Growth factors	9	12
Hydroxyurea	13	18
Intensive chemotherapy	12	16

2. Patients and methods

Seventy-six consecutive patients fulfilling WHO classification criteria for CMML, treated with azacitidine between 2004 and 2009 in 3 programs (French AZA compassionate program, Cleveland Clinic and H. Lee Moffitt Cancer Center) were retrospectively reviewed.

US patients received azacitidine following FDA approval. Following this approval and before European Medicine Agency (EMA) approval in 2008, the French health agency (AFSSAPS) opened a compassionate patient-named program of AZA in higher risk MDS including CMML, in cooperation with the Groupe Francophone des Myelodysplasies (GFM). The CMML part of that program corresponded to the French patients included in this paper. Retrospective analyses of patient data were approved by local Institutional Review Board (Cleveland Clinic, H. Lee Moffitt Cancer Center and GFM). CMML was defined as patients having persistent peripheral blood monocytosis >1 × 10^9/L, without Philadelphia chromosome or BCR-ABL fusion gene, <20% blasts in the blood and bone marrow and dysplasic features in one or more myeloid lineages.

All patients received azacitidine for at least one cycle (75 mg/m^2/day during 5–7 days, every 28 days). Response was evaluated according to IWG 2006 criteria, but also took into account evolution of "proliferative" features of CMML (including palpable splenomegaly and white blood cell count in patients with WBC > 13 G/L).

Baseline characteristics and response rates were compared by nonparametric tests (exact Fisher test for qualitative variables, Kruskal–Wallis test for quantitative variables). Censored endpoints were estimated by the non-parametric Kaplan–Meier method, and compared by the log-rank test. Survival was measured from the onset of hypomethylating agent therapy. Type I error was fixed at the 5% level. All tests were two-tailed. Statistical analysis was performed on StataSE 10.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Baseline patient characteristics

Between 2004 and 2009, 76 CMML patients received azacitidine in France, at Cleveland Clinic and at H. Lee Moffitt Cancer Center. Patient characteristics are summarized in Table 1. They included 47 males and 29 females, and median age was 70 years (range, 33–85). Interval from diagnosis to treatment was less than 6 months in 42% of the patients, between 6 and 12 months in 14% and more than 12 months in 44%. At onset of azacitidine, median WBC, hemoglobin level and platelet count were 11.4 G/L, 10 g/dL (range 6.3–15.2) and 59 G/L (range 9–1214), respectively. According to WHO classification, 55% of the patients had CMML1 and 45% CMML2. Karyotype was normal (55%), with chromosome 5 and/or 7 abnormalities (10%), and with other cytogenetic changes (21%). Forty six percent of the patients had WBC count above 13 × 10^9/L (MPN-CMML) and 32% had palpable splenomegaly. Overall, 44% patients had neither splenomegaly nor WBC > 13 × 10^9/L, 32% patients had one of those features and 23% had both. Among patients with WBC < 13 × 10^9/L, IPSS was Low or Intermediate-1 in 46% and Intermediate-2 or High in 54%.

Prior to azacitidine, 46% of the patients had received treatment, including growth factors in 12%, hydroxyurea in 18%, and intensive, cytarabine-based chemotherapy in 16% of the patients.

3.2. Treatment results

The median number of cycles of AZA administered was 6 (range 1–40) and median follow up from onset of treatment was 3 years.

Thirty-three patients (43%) achieved a response according to IWG 2006 criteria, including 13 complete remissions (CR) (17%), 1 partial remission (PR) (1.3%), 6 marrow CR (8%) and 13 additional patients fulfilling criteria for stable disease with hematological improvement (HI) (17%). Of the 60 patients who received at least 4 cycles of azacitidine, 33 (55%) responded, including 13 (22%) CR. Only age (median 71.4 vs. 66.5 years in responders vs. non responders, respectively, $p = 0.014$) significantly influenced the response rate, while WBC count analyzed continuously, ($p = 0.54$), WBC > 13 × 10^9/L ($p = 0.63$), hemoglobin level ($p = 0.40$), platelet count ($p = 0.23$), bone marrow blast percentage ($p = 0.32$), presence of splenomegaly ($p = 0.44$), cytogenetics ($p = 1.0$), disease duration ($p = 0.8$) and prior therapy ($p = 0.193$) had no impact on response achievement. When the analysis was restricted to patients who achieved CR, marrow CR or PR (excluding patients with isolated HI), or stratified on the presence or absence of proliferative features (WBC > 13 G/L and splenomegaly), similar results were found, with none of the previous parameters influencing response.

Twenty-four patients progressed to AML, after a median of 1.2 years from azacitidine initiation, including 11 of the 33 responders. There was a trend for higher WBC count (24.8 vs. 16 G/L, $p = 0.07$) and having splenomegaly (47% vs. 26%, $p = 0.13$) at baseline in patients who progressed while other factors, including bone marrow blast percentage, had no influence on the risk of leukemic evolution among these patients treated with azacitidine.

Median survival was 29 months. In univariate analysis (Table 2), palpable splenomegaly (median 1.2 vs. 2.4 years, $p = 0.02$) (Fig. 1B), WBC > 13 × 10^9/L (median 1.2 vs. 2.4 years, $p = 0.039$) (Fig. 1A), IPSS in patients with WBC < 13 G/L (median 3 years for low/int1 vs. 1.9 year for high/int 2, $p = 0.006$), bone marrow blasts >10% ($p = 0.05$) significantly influenced OS while karyotype ($p = 0.46$), sex ($p = 0.32$) and prior therapy including ($p = 0.32$) or excluding growth factors ($p = 0.07$) had no significant influence on OS.

Combining palpable splenomegaly and WBC > 13 × 10^9/L allowed to discriminate OS between patients with none (median OS 2.4 years), one (2 years) or both of those parameters (1.1 year, $p = 0.0054$, Fig. 1C). After 2 years, only 12 patients were still alive. Only one of them had baseline WBC > 13 × 10^9/L and one had splenomegaly. None of the patients who survived more than 2 years had both proliferative features.

By multivariate analysis, only marrow blasts >10% (HR = 2.16 (1.10–4.23), $p = 0.02$) and palpable splenomegaly (HR = 2.26 (1.1–4.5), $p = 0.024$) had prognostic impact on OS. When the