Original Article

Activity of Azacitidine in Chronic Myelomonocytic Leukemia

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BACKGROUND: Hypomethylating drugs are useful in the management of myelodysplastic syndrome (MDS). Two of these drugs, azacitidine and decitabine, have received FDA approval for the treatment of MDS and chronic myelomonocytic leukemia (CMML). However, phase 2 and 3 studies that assessed these agents in MDS included only a small number of patients with CMML. The objective of this study was to evaluate the efficacy and safety of azacitidine in the treatment of CMML. **METHODS:** The records of thirty-eight patients diagnosed with CMML and treated with azacitidine at our institution were reviewed. Azacitidine was administered at 75 mg/m^2/day for 7 days or 100 mg/m^2/day for 5 days every 4 weeks. Patients who received at least 1 cycle of the drug were considered evaluable for response. **RESULTS:** Response was assessed by the modified International Working Group (IWG) criteria. The overall response rate was 39% (14 of 36); complete response (CR) rate was 11% (4 of 36); partial response (PR) rate was 3% (1 of 36); hematologic improvement (HI) was 25% (9 of 36). The median overall survival was 12 months. There was a statistically significant overall survival advantage in responders compared with nonresponders: 15.5 months versus 9 months, respectively ($P = .04$). Treatment was generally well tolerated. One of 2 patients had complete resolution of a skin rash that was due to monocytic infiltration. **CONCLUSIONS:** Azacitidine is active in the treatment of CMML. The therapy-associated toxicity is acceptable. Our results support further investigation of azacitidine in CMML, particularly in combination with other agents. ***Cancer* 2011;117:2690–6.** © *2010 American Cancer Society.*

KEYWORDS: azacitidine, CMML, MDS, hypomethylating agents, decitabine.

Chronic myelomonocytic leukemia (CMML) is a bone marrow disorder characterized by myeloproliferative and myelodysplastic features. In the French-American-British (FAB) classification, this disease was considered a myelodysplastic disorder.[1] Subsequently, this classification was modified to acknowledge a myeloproliferative and myelodysplastic form of this disorder. A white blood cell count (WBC) of 13×10^9/L or greater was used to define MPD-CMML, whereas a lower WBC defined MDS-CMML.[2] In the World Health Organization (WHO) classification of 2001, CMML was reclassified as a myelodysplastic/myeloproliferative entity.[3] An update of the WHO classification in 2008 subdivided CMML into CMML-1 with <10% bone marrow (BM) and <5% peripheral blood (PB) blasts and CMML-2 with 10%-19% BM and/or 5%-19% PB blasts.[4]

CMML is a disease of the elderly. The median age at diagnosis is 72 years.[5] It commonly presents with cytopenia, monocytosis, and splenomegaly. Diagnostic criteria include a persistent peripheral blood monocyte count $>1 \times 10^9$/L; dysplasia in 1 or more hematopoietic cell lines, and up to 19% peripheral blood and bone marrow blasts. The prognosis is quite variable. The median overall survival from the time of diagnosis was 19 months in 288 patients included in a German MDS registry.[5] In another series of 213 patients reported by Onida et al, it was only 12 months.[6] This poor survival reflected not only the natural history of this disease but also the need for more effective therapy. Several study groups have attempted to create a prognostic scoring system for CMML.[6-8] Beran et al were the only investigators able to develop a prognostic model that was subsequently validated in a prospective study. In their analysis, hemoglobin, number of bone marrow blasts, presence of circulating immature myeloid cells, and absolute lymphocyte count were identified and confirmed as independent prognostic variables. They were able to stratify patients into 4 survival categories accordingly.[6,9]

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DOI: 10.1002/cncr.25759, **Received:** February 11, 2010; **Revised:** September 10, 2010; **Accepted:** October 4, 2010, **Published online** December 23, 2010 in Wiley Online Library (wileyonlinelibrary.com)

Criteria for initiation of therapy in CMML are not well established. Treatment is commonly initiated for signs or symptoms such as fever, weight loss, painful splenomegaly, cytopenia, transfusion dependence, organ involvement, increasing number of blasts, and the physician's experience.

To date, allogeneic hematopoietic stem cell transplantation is the only therapeutic modality that can offer prolonged remission or even cure. However, most patients are not candidates for an allogeneic transplant because of their age of presentation or a comorbidity. Moreover, disease relapse still remains an issue in these patients.[10-12]

Common drugs used in treatment include growth factors, hydroxyurea,[13] oral etoposide,[13] low-dose cytarabine, and oral topotecan.[14-16] Imatinib mesylate appears to be highly effective in the occasional CMML patient who has a chromosomal translocation involving the platelet-derived growth factor receptor-beta gene.[17,18]

Two hypomethylating agents, azacitidine and decitabine, are the only 2 US Food and Drug Administration (FDA)-approved agents for the treatment of CMML. These 2 drugs have shown activity in trials primarily designed to test their efficacy in treatment of myelodysplastic syndromes where CMML represented a minority of the study population. Less than 10 patients with CMML were treated with each of the 2 drugs in the pivotal phase 3 studies.[19,20] We present our experience with azacitidine in the treatment of CMML.

MATERIALS AND METHODS

Patients

The charts of patients with a diagnosis of CMML who were treated with azacitidine at our institution from 1996-2008 were retrospectively reviewed. Thirty-eight patients with up to 19% peripheral and bone marrow blasts and a peripheral blood monocyte count $>1 \times 10^9$/L were judged by the WHO classification as having CMML. A total of twenty-nine patients were enrolled in the azacitidine compassionate-use program through the National Cancer Institute (NCI) from 1996-2004. Azacitidine was approved by the US FDA in 2004 and became commercially available. Between 2004 and 2008, 9 patients received azacitidine off protocol at our institution. Two were not evaluable because they had received <1 cycle of azacitidine. Although only patients who met WHO criteria for diagnosis were entered in the study, the FAB system also was used in classification to evaluate the response to azacitidine in the 2 FAB subtypes.

Methods

A total of 29 patients were enrolled in the azacitidine compassionate-use program through the NCI. They received azacitidine at a dose of 75 mg/m^2/day for 7 consecutive days via subcutaneous injection. This cycle was repeated every 28 days for as long as therapy was tolerated and response was maintained. The first injection was given in an outpatient setting where these patients were under observation. Subsequent injections were self-administered at home. An oral 5-HT3 antagonist was given as an antiemetic before each injection. Compliance was assessed verbally and by counting syringes that were returned for disposal. Dose adjustment was based on peripheral blood counts and bone marrow cellularity according to the dose-adjustment schedule of CALGB 9221.[19] Erythropoiesis-stimulating agents (ESA) administration was not allowed for the patients treated on this program (in compliance with CALGB 9221 protocol).

A total of 9 patients received commercially available azacitidine at a dose of 100 mg/m^2/day for 5 consecutive days via subcutaneous injection. Although this dose had not previously been tested, we believed that a 5-day dosing (100 mg/m^2/daily) would be roughly equivalent to a 7-day dosing (75 mg/m^2/daily). The total dosing schedule was planned to be 500 mg/m^2 versus 525 mg/m^2 for the 5-day and 7-day schedules, respectively. The 5-day schedule was considered more convenient. The treatment was given at our institution on an outpatient basis. The treatment was repeated every 28 days for as long as it was tolerated and response was maintained. Two patients were not evaluable for response given the finding that they received <1 cycle.

For patients treated off-protocol, no dose adjustments for hematologic toxicity were made before cycle 4 unless life-threatening complications occurred due to myelosuppression. ESA administration was allowed for patients treated off protocol. Dose adjustments were made for grade 3 of 4 nonhematologic toxicity. Transfusion of blood products was allowed. Antibiotic prophylaxis and growth factors were used when deemed necessary by the treating physician.

Response Criteria

Response was assessed by modified IWG criteria.[21] Complete remission (CR) was defined as BM blast count $\leq 5\%$ with normal maturation of all cell lines for at least 4 weeks. In addition, the presence of a PB neutrophil count of $\geq 1.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥ 11 g/dL, and no PB blasts were required. Partial

response (PR) required that all criteria for CR be met, except BM blasts decreased by ≥50% over pretreatment but still >5%. Stable disease (SD) was defined as failure to achieve at least PR and no evidence of progression for >8 weeks.

Patients not achieving at least PR were further assessed for hematological improvement (HI) by using the IWG criteria for MDS. Hematologic improvement (HI) was reported as follows: erythroid response required a hemoglobin increase by at least 1.5 g/dL or reduction in transfusion requirements. If baseline platelets were $<20 \times 10^9$/L, a response required an increase by at least 100% and to more than 20×10^9/L. If baseline platelets were more than 20×10^9/L, a response required an absolute increase of at least 30×10^9/L. Neutrophil response referred to a granulocyte increase by at least 100% over baseline and by an absolute increase of at least 0.5×10^9/L. Progressive disease (PD) was defined as a ≥50% increase in BM blast cells or at least 50% decrement from maximum response in granulocytes and platelets, reduction in hemoglobin by ≥2 g/dl and transfusion dependence. HI had to be sustained for at least 8 weeks. Bone marrow aspirates and biopsies were reviewed by pathologists at our institution and response was assessed by 2 of the authors. Overall response rate (ORR) was defined as the sum of CR, PR, and HI. Survival was measured from the start of therapy.

Statistical analysis

Statistical analyses were performed using Stata SE 10.0 software (StataCorp, College Station, Tex). Data were summarized using median, range, and percentage. Data were compared in relation to the overall response and other key variables. All categorical variables were compared using Fisher exact test. Continuous variables were examined for normality before analysis. Differences were tested using Wilcoxon rank-sum nonparametric test. Survival in each group is estimated by the Kaplan-Meier method and compared using the log-rank test. All tests were 2-sided with significance set at $P<.05$.

RESULTS

The patient baseline characteristics are shown in Table 1. The male to female ratio was 4:1. The median age of our cohort was 70.5 years (range, 36-83 years). Median age for males was 71 years (range, 36-83 years). Median age for females was 69 years (range, 46-79 years). Overall, eleven (30%) patients had WBC $\leq 13 \times 10^9$/L and were considered to have MDS-CMML. The other 25 (70%) patients had MPD-CMML according to FAB classification. Twenty-six (73%) patients had CMML-1; 9 (27%) had CMML-2 according to WHO classification. The number of bone marrow blasts was indeterminate in 1 patient due to a lack of spicules in the bone marrow aspirate. Ten patients in the study had splenomegaly. Two patients had skin rash, with evidence of monocytic infiltration on biopsy.

Table 1. Characteristics of Patient Group

Characteristics		No. (%)
Age, y	Median	70.5
Sex	Female	7 (19)
Splenomegaly	Yes	10 (28)
WBC x 10^9/L	≤13	11 (31)
	>13	25 (69)
Cytogenetics	Good	19 (53)
(IPSS)	Intermediate	13 (36)
	Poor	3 (8)
	Not performed	1 (3)
% Marrow blasts	<10	26 (72)
	≥10	9 (25)
	Not known	1 (3)
Duration of disease, mo	<6	25 (69)
	6-12	5 (14)
	>12	6 (17)
Prior therapy for CMML	None	16 (44)
	Hydroxyurea	11 (31)
	G-CSF	3 (8)
	Erythropoetin	4 (11)
	Others	7 (19)
Secondary CMML	Yes	3 (8)
Skin involvement	Yes	2 (6)

IPSS indicates International Prognostic Scoring System; CMML, chronic myelomonocytic leukemia.

Stratification by the International Prognostic Scoring System (IPSS)[22] was as follows: high (n = 4), intermediate-2 (n = 7), intermediate-1 (n = 16), low (n = 6), undetermined (n = 3). IPSS could not accurately be calculated in these 3 patients because of an inadequate marrow specimen, which precluded accurate blast percentage determination in 1 case (IPSS at least intermediate-2); the absolute neutrophil count was not determined in a second case (IPPS at least intermediate-2); karyotype information was not available in a third case (IPSS at least intermediate-1). Secondary CMML was present in 3 patients. Cytogenetic stratification before the initiation of therapy according to IPSS was as follows: good (n = 19), intermediate (n = 13), poor (n = 3). No cytogenetic abnormalities were found in 18 patients. Abnormalities of chromosome 7 were present in 3 patients. No patient had chromosome 5 abnormalities.

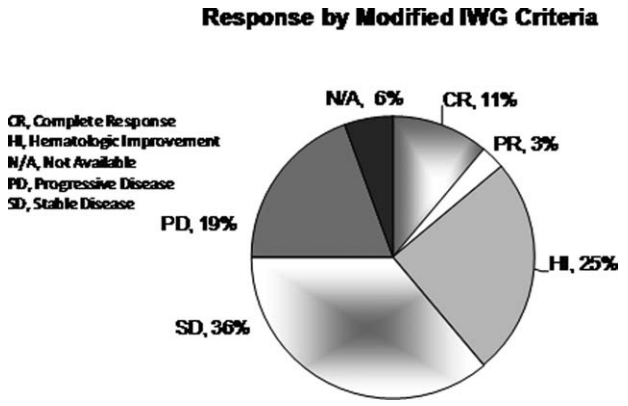

Figure 1. Response by modified International Working Group (IWG) criteria.

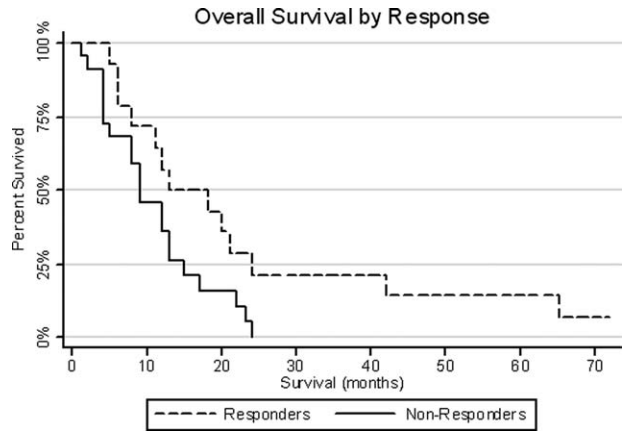

Figure 2. Overall survival by response.

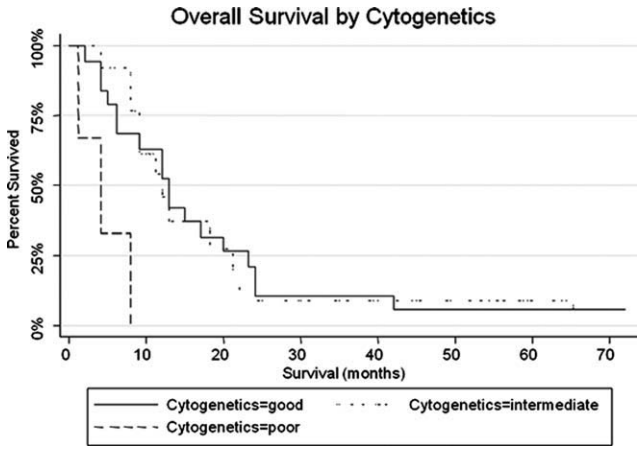

Figure 3. Overall survival by cytogenetics.

Pathology and responses were assessed internally at our institution. Overall response rate was 39% (14 of 36 patients). Response was stratified as follows: CR rate was 11% (4 of 36 patients), PR rate was 3% (1 of 36 patients), and HI rate was 25% (9 of 36 patients). Furthermore, 13 (36%) patients had stable disease (Fig. 1). The median number of cycles given was 5 (range, 1 to >50 cycles). In those who achieved response, the median duration of response was 6.5 months (range, 3 to >50 months). The median number of cycles given to achieve response was 2 (range, 1-6 cycles).

Response was observed in 32% (8 of 25 patients) with MPD-CMML and in 55% (6 of 11 patients) with MDS-CMML ($P = .3$). The overall response rate was 56% (5 of 9 patients) in CMML-2 and 35% (9 of 26 patients) in CMML-1 ($P = .7$). Of the 10 patients who had splenomegaly on presentation, 4 (40%) experienced decrease in spleen size. However, 3 of those were receiving hydroxyurea contemporaneously. One of the 2 patients with skin involvement by a monocytic infiltrate had complete resolution of the rash after 4 cycles of azacitidine. The other underwent external beam radiation for symptom control.

Eight of 15 patients that were considered responders had abnormal conventional cytogenetics. Follow-up cytogenetic data were available for 6 of them, and they all had a cytogenetic response. The cytogenetic abnormalities found in these patients were: del 17q (n = 1); −Y (n = 1); del 16q, +13 (n = 1); +8 (n = 1); del 16q, +22 (n = 1); +11(n = 1).

The median overall survival of patients was 12 months (range, 1-72 months). There was a statistically significant overall survival difference between responders and nonresponders: 15.5 (range, 5-72 months) versus 9 months (range, 1-24 months), respectively ($P = .04$; Fig. 2). The median survival for those with good, intermediate, and poor risk cytogenetics was 13 months (range, 2-72 months), 12 months (range, 4-65 months), and 4 months (range, 1-8 months), respectively ($P = .005$; Fig. 3). The median survival for patients with MDS-CMML was 23 months (range, 4-72 months) compared with 12 months (range, 1-42 months) for patients with MPD-CMML ($P = .02$; Fig. 4). The median survival was 12 months for CMML-1 and 11months for CMML-2 ($P = .3$).

Toxicity

The major toxic events are depicted in Table 2. Side effects from azacitidine were acceptable in most patients. A total of 6 patients experienced no toxicity. Mild site-

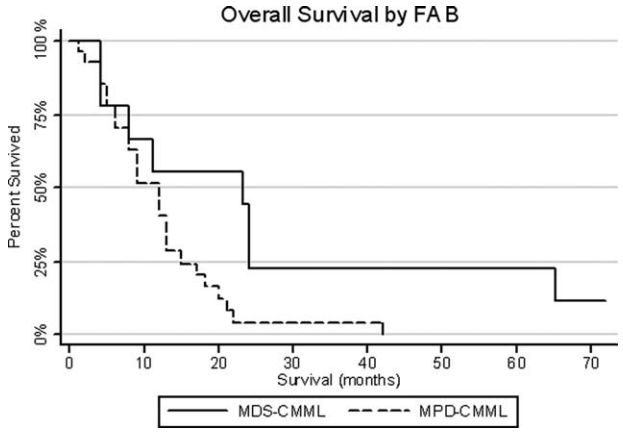

Figure 4. Overall survival by Frech-American-British (FAB). MDS-CMML indicates myelosdysplatic chronic myelomonocytic leukemia; MPD-CMML, myeloproliferative chronic myelomonocytic leukemia.

injection irritation occurred in 4 patients and did not result in dose modification or cessation of therapy. Other common nonhematologic toxicities were fatigue, anorexia, and skin rash. While on therapy with azacitidine, 2 patients experienced febrile neutropenia, and 4 patients developed pneumonia. Three episodes of gastrointestinal (GI) bleed were observed and treated appropriately. One patient died of septic shock while on treatment.

DISCUSSION

An epigenetic approach to therapy seems to be biologically justifiable in the treatment of CMML because aberrant methylation of an important cell-regulation gene p15 (INK4b) was demonstrated in this disease.[23] Both azacitidine and decitabine are incorporated into DNA and produce a marked decrease in the activity of DNA methyltransferase.[24]

Initial reports of efficacy of hypomethylating agents in the treatment of CMML came from studies on MDS patients. In the report by Silverman et al, a total of 7 patients with CMML received azacitidine.[19] In data published by Kantarjian et al, only 6 patients with CMML received decitabine.[20] These 2 studies, despite the small number of patients with CMML, constitute the basis of the FDA approval for these 2 drugs in the treatment of CMML.

Wijermans et al later reported on the outcome of patients with CMML treated with decitabine. The data were pooled from the 3 multicenter phase 2 studies and the multicenter phase 3 study for patients with MDS and CMML.[20,25-27] Thirty-one patients with CMML were enrolled in these studies. The overall response rate according to IWG criteria was 37% (10% CR + 16% PR + 11% HI).[28]

Table 2. Toxicity Data

Toxicity	No.
Fatigue	6
Site irritation	4
Septic shock	1
Pericardial effusion	1
Febrile neutropenia	2
Rash	3
Cytopenia	9
Pneumonia	4
GI bleed	3
Anorexia	4

Further data to support the use of hypomethylating agents in the treatment of CMML came from the report by Aribi et al. In their series, a total of 19 patients with CMML received decitabine. The response rate was 69% (58% CR + 11% HI).[29,30] Recently, Iastrebner et al reported a response rate of 35% (23% CR + 8% HI + 4% marrow CR) in 26 CMML patients treated with decitabine in an international multicenter study.[31] The difference in response rate between the 2 studies likely represented the differences between single and multi-institutional experiences.

Another phase 3 randomized trial comparing azacitidine to conventional care in the treatment of higher risk myelodysplastic syndrome showed improved overall survival for those patients in the experimental arm. This study included 11 patients with CMML that received azacitidine, but response was not reported for that patient population specifically.[32]

In this article, we retrospectively analyzed the response to 2 schedules of azacitidine in patients with CMML at our institution. This data shows encouraging activity of azacitidine in CMML with an overall response rate of 39%. This response demonstrated a statistically significant difference in overall survival between responders and nonresponders. Interestingly, response rate was lower in patients with MPD-CMML. Furthermore, median survival in our study was shorter than survival reported in some registries,[5] and that could be due to the finding that 70% of our patients had MPD-CMML subtype, which has been associated with shorter overall survival in several reports.[5,33]

The IWG criteria do not address response in terms of cytoreduction in MPD-CMML or in extramedullary manifestations; hence, some of our patients with MPD-CMML were considered to have stable disease despite decrease in their WBCs. Although we observed response

to azacitidine with extramedullary manifestations, the numbers were too small to draw definitive conclusions.

In general, the drug was well tolerated with acceptable hematologic and nonhematologic toxicity in most patients. Toxicities were similar to those observed in other analyses that had used azacitidine.[34] However, toxicities could not be assessed according to NCI common toxicity criteria because these data were not collected while patients were receiving treatment.

Our data have some limitations given that they represent a single-institution retrospective analysis. Moreover, patients receiving azacitidine off-protocol were allowed to receive ESA and growth factors at a treating physician's discretion, which could have influenced hematologic responses. Only 1 of these patients had HI. This patient had erythroid response as well as a decrease in monocyte count to $<1 \times 10^9$/L and a decrease in BM blasts from 9% to 5%.This HI was not included in the overall response rate given his treatment with ESA. We surmised that a previously untested dose of 100 mg/m^2 daily for 5 days would have a more convenient schedule and would be roughly equivalent to the FDA-approved dose.

Although both azacitidine and decitabine seem to be effective in CMML, it is hard to draw conclusions regarding superiority of 1 over the other because there has been no direct comparison between them. Moreover, it would be problematic to compare survival across studies given differences in patient populations.

The 2 drugs appear to be a promising treatment platform upon which to build new treatment combinations for CMML. For instance, the combination of DNA methyltransferase and histone deacetylase inhibition was shown to be promising in the treatment of myeloid neoplasms.[35] Other attractive regimens to be studied include azacitidine and thalidomide, as this regimen has shown a response rate of greater than 50% for the treatment of MDS and AML,[36] or azacitidine and farnesyl transferase inhibitors.[37]

In conclusion, azacitidine appears to be active in the treatment of CMML. The activity and toxicity profiles seem favorable. Combinations using azacitidine and novel agents could be tested in randomized trials to further improve survival and response rates in CMML.

CONFLICT OF INTEREST DISCLOSURES

James M. Rossetti is part of the bureau of speakers for Celgene, Millennium Pharmaceuticals and Merck. Entezam A. Sahovic is part of the bureau of speakers for Alexion, Celgene, and Millennium Pharmaceuticals. Richard K. Shadduck and Joan Latsko are part of the bureau of speakers for Celgene.

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