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ORIGINAL REPORT

Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia

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ABSTRACT

Purpose
In a phase III randomized trial, azacitidine significantly prolonged overall survival (OS) compared with conventional care regimens (CCRs) in patients with intermediate-2– and high-risk myelodysplastic syndromes. Approximately one third of these patients were classified as having acute myeloid leukemia (AML) under current WHO criteria. This analysis compared the effects of azacitidine versus CCR on OS in this subgroup.

Patients and Methods
Patients were randomly assigned to receive subcutaneous azacitidine 75 mg/m^2/d or CCR (best supportive care [BSC] only, low-dose cytarabine (LDAC), or intensive chemotherapy [IC]).

Results
Of the 113 elderly patients (median age, 70 years) randomly assigned to receive azacitidine (n = 55) or CCR (n = 58; 47% BSC, 34% LDAC, 19% IC), 86% were considered unfit for IC. At a median follow-up of 20.1 months, median OS for azacitidine-treated patients was 24.5 months compared with 16.0 months for CCR-treated patients (hazard ratio = 0.47; 95% CI, 0.28 to 0.79; $P = .005$), and 2-year OS rates were 50% and 16%, respectively ($P = .001$). Two-year OS rates were higher with azacitidine versus CCR in patients considered unfit for IC ($P = .0003$). Azacitidine was associated with fewer total days in hospital ($P < .0001$) than CCR.

Conclusion
In older adult patients with low marrow blast count (20% to 30%) WHO-defined AML, azacitidine significantly prolongs OS and significantly improves several patient morbidity measures compared with CCR.

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INTRODUCTION

Acute myeloid leukemia (AML) is associated with poor prognosis in elderly patients,[1-3] with 2- and 5-year overall survival (OS) rates of approximately 10% and 2%, respectively.[4-6] There are no truly adequate treatments for AML patients.[7] Intensive chemotherapy (IC) is often inappropriate as a result of poor performance status, significant comorbidities, adverse tumor cytogenetics, and poor treatment tolerability, leading to treatment-related mortality rates of 10% to 25%.[8-12] Treatment with IC is generally limited to 30% to 60% of older AML patients.[13] Low-dose cytarabine (LDAC), the farnesyltransferase inhibitor tipifarnib, and gemtuzumab ozogamicin have demonstrated limited impact on survival, whereas the survival impact of new drugs (eg, clofarabine) remains unproven.[14-17] Even IC, when feasible, is associated with a median survival of only 5 to 13 months.[11,17-19] Therefore, new treatment options are needed for these patients.

In a recent phase III trial, azacitidine (Vidaza; Celgene Corporation, Summit, NJ) demonstrated significantly prolonged OS compared with conventional care regimens (CCRs) in patients with International Prognostic Scoring System–classified intermediate-2– and high-risk myelodysplastic syndromes (MDSs).[20] This study used the French-American-British (FAB) classification for MDS[21] and included approximately one third of patients with refractory anemia with excess blasts in transformation (RAEB-t; 20% to 30% bone marrow [BM] blasts). WHO criteria now define AML as ≥ 20% BM blasts.[22-25] Using those criteria, RAEB-t is now

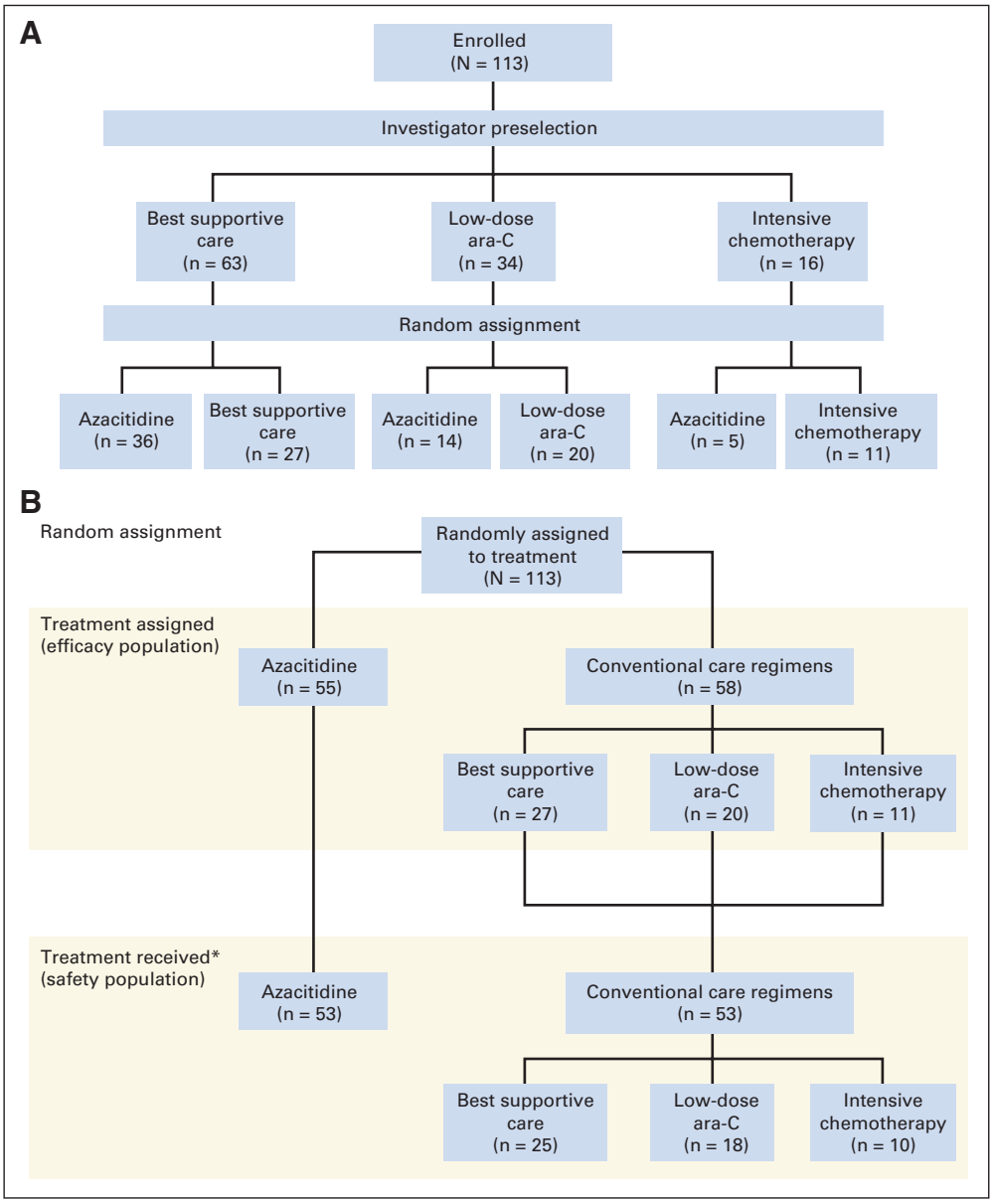

Fig 1. CONSORT diagram showing (A) patient enrollment and investigator preselection of conventional care regimen and (B) subsequent random assignment to treatment and treatment received. (*) Seven patients withdrew from the study before receiving treatment and were not included in the safety population; two of the patients were from the azacitidine group, and five were from the conventional care regimen group (best supportive care, n = 2; low-dose cytarabine [ara-C], n = 2; and intensive chemotherapy, n = 1).

considered as AML. This analysis compared the relative efficacy and safety of azacitidine versus CCR in this patient subgroup.

PATIENTS AND METHODS

Study Design and Patients

The primary study was a phase III, international, multicenter, randomized, controlled, parallel-group trial.[20] The present analysis included patients with ≥ 20% BM or peripheral blasts based on central BM review (ie, with FAB-defined RAEB-t and WHO-defined AML).[21,22-25] Additional eligibility criteria included age ≥ 18 years, Eastern Cooperative Oncology Group performance status of 0 to 2, and an estimated life expectancy of ≥ 3 months. Patients with therapy-related disease; prior treatment with azacitidine, decitabine, or chemotherapy; or planned allogeneic stem-cell transplantation were excluded. Detailed methodology has been previously reported.[20] Briefly, before random assignment, investigators selected one of three CCRs (best supportive care [BSC] only, LDAC, or anthracycline plus cytarabine–based IC) for patients based on age, Eastern Cooperative Oncology Group performance status, and comorbidities (Fig 1). This was an individually based choice that could take into account institutional, regional, or national guidelines.[26,27] Patients were then randomly assigned to receive azacitidine or the preselected CCR. No crossover was permitted, and use of erythropoietin or darbepoetin was not allowed.

Azacitidine was administered subcutaneously (75 mg/m^2/d) for 7 days of every 28-day cycle, for at least six cycles. BSC included blood product transfusions and antibiotics with granulocyte colony-stimulating factor for neutropenic infection. LDAC was administered subcutaneously (20 mg/m^2/d) for 14 days of every 28-day cycle, for at least four cycles. IC consisted of induction with cytarabine (100 to 200 mg/m^2/d by continuous infusion) for 7 days plus daunorubicin (45 to 60 mg/m^2/d), idarubicin (9 to 12 mg/m^2/d), or mitoxantrone (8 to 12 mg/m^2/d) for 3 days. Patients with complete remission (CR) or partial remission were administered one or two consolidation courses of the same cytotoxic therapy used for induction at reduced doses, followed by BSC. Treatment with azacitidine or LDAC was delayed as appropriate for blood count recovery. All patients could receive BSC, and all treatment regimens

were administered until study end or patient discontinuation as a result of disease progression, unacceptable toxicity, or BM blasts more than 30% with a 50% increase from the pretreatment blast count.

Assessment of Efficacy and Safety

The primary study end point was OS compared between the azacitidine and combined CCR treatment groups. A supportive analysis to the primary end point compared OS between azacitidine and each of the three individual treatments comprising CCR and was based on investigator preselection. Additional supportive analyses compared OS between azacitidine and combined CCR groups in patients considered unfit for IC (ie, preselected to receive BSC or LDAC) and assessed the potential influence of cytogenetics on OS. In the absence of consensus for cytogenetic classification of AML in elderly patients,[10] we reclassified patients as having favorable [inv16, t(8,21)], unfavorable (−7/7q– or complex), or intermediate (all others including normal) karyotypes. However, this did not lead to any changes between cytogenetic groups because no patient had a favorable karyotype.

Secondary end points were morphologic CR assessed according to International Working Group AML response criteria,[28] transfusion independence (absence of RBC or platelet transfusions during 56 consecutive days), adverse events (assessed using National Cancer Institute Common Toxicity Criteria, version 2.0), rate of fever requiring intravenous antibiotics, and hospitalization rates and duration.

Statistical Analysis

The first patient's informed consent was received on November 24, 2003; the data cutoff date was July 24, 2007. Efficacy analyses included all randomly assigned patients with WHO-defined AML (≥ 20% BM blasts). OS was defined as time from random assignment until death from any cause and was assessed using the Kaplan-Meier method and Cox proportional hazards model stratified on the randomized factors of FAB and International Prognostic Scoring System with model term of treatment.[21,29] Patients were observed until death or study closure. Patients alive at study closure were censored at date of last observation. Treatment effect consistency across preselection groups was assessed by testing the difference in likelihood ratio between two models (treatment × preselection interaction terms and treatment alone). The end point used was OS, and homogeneity refers to the homogeneity of hazards of death (or hazard ratio [HR]; azacitidine *v* CCR) across preselection groups.

Response rates were compared for the azacitidine and CCR groups using Fisher's exact test. Safety analyses were performed in patients who received at least one dose of study drug and had one or more postdose safety assessment. Comparisons of transfusion independence, hospitalization, and antibiotic use were analyzed using two approaches: azacitidine versus CCR including patients preselected for IC and azacitidine versus CCR excluding patients preselected for IC.

RESULTS

Patient Characteristics

The study population included 113 patients randomly assigned in the original phase III study who met WHO-AML criteria.[20] Of these, two patients had BM counts of 34% and 69%. All 113 patients were included in this intent-to-treat analysis. The efficacy population included 55 patients randomly assigned to azacitidine and 58 patients randomly assigned to CCR. Of the 58 patients in the CCR group, 27

Table 1. Baseline Patient Demographics and Disease Characteristics by Treatment Group and Investigator Preselection

	All Patients (N = 113)				BSC Only (n = 73)				LDAC (n = 34)				Intensive Chemotherapy (n = 16)			
	Azacitidine (n = 55)		CCR (n = 58)		Azacitidine (n = 36)		BSC Only (n = 27)		Azacitidine (n = 14)		LDAC (n = 20)		Azacitidine (n = 5)		Intensive Chemotherapy (n = 11)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years																
Median	70		70		70		70		69		71		63		65	
Range	52-80		50-83		52-80		56-81		55-78		56-83		53-78		50-76	
45-54	3	5.5	1	1.7	2	5.6	0		0		0		1	20.0	1	9.1
55-64	12	21.8	9	15.5	7	19.4	3	11.1	3	21.4	3	15.0	2	40.0	3	27.3
65-74	28	50.9	29	50.0	17	47.2	14	51.9	10	71.4	9	45.0	1	20.0	6	54.5
≥ 75	12	21.8	19	32.8	10	27.8	10	37.0	1	7.1	8	40.0	1	20.0	1	9.1
Male	37	67.3	41	70.7	21	58.3	16	59.3	13	92.9	15	75.0	3	60.0	10	90.9
Cytogenetic risk group																
Intermediate	38	69.1	43	74.1	24	66.7	19	70.4	9	64.3	18	90.0	5	100	6	54.5
Normal	19	34.5	33	56.9	13	36.1	12	44.4	5	35.7	15	75.0	1	20.0	6	54.5
Unfavorable	14	25.5	13	22.4	9	25.0	8	29.6	5	35.7	1	5.0	0		4	36.4
Missing	3	5.5	2	3.4	3	8.3	0		0		1	5.0	0		1	9.1
ECOG score																
0	16	29.1	22	37.9	9	25.0	5	18.5	5	35.7	12	60.0	2	40.0	5	45.5
1	35	63.6	34	58.6	23	63.9	21	77.8	9	64.3	7	35.0	3	60.0	6	54.5
2	4	7.3	0		4	11.1	0		0		0		0		0	
Missing	0		2	3.4	0		1	3.7	0		1	5.0	0		0	
Bone marrow blasts, %																
Median	23.0		23.1		22.5		23.0		24.2		22.0		26.0		27.0	
Range	20.0-34.0		13.0-68.9*		20.0-29.4		13.0-29.2*		20.0-34.0		20.0-28.0		22.0-28.0		21.0-68.9	
Transfusion dependent																
Red blood cells	34	61.8	39	67.2	22	61.1	22	81.5	10	71.4	12	60.0	2	40.0	5	45.5
Platelets	15	27.3	10	17.2	9	25.0	4	14.8	5	35.7	6	30.0	1	20.0	0	

Abbreviations: BSC, best supportive care; LDAC, low-dose cytarabine; CCR, conventional care regimen; ECOG, Eastern Cooperative Oncology Group.
*One patient (BSC only) had a bone marrow blast count of 13% but was included in the study based on a peripheral blast count of 20%.

(47%), 20 (34%), and 11 (19%) were preselected by their treating physicians to receive BSC only, LDAC, and IC, respectively.

Baseline characteristics were comparable between the two treatment groups (Table 1). Median age was 70 years, and the median BM blast count was 23% in both groups. Three patients (azacitidine, n = 1; BSC, n = 1; LDAC, n = 1) had chronic myelomonocytic leukemia (CMML) with more than 20% BM blasts. Three patients (all CMML) had a WBC count of more than 10×10^9/L at baseline (azacitidine, n = 1; CCR, n = 2). Overall, 24% of patients had an unfavorable karyotype (−7/7q– or complex; azacitidine, 25%; CCR, 22%), and 72% of patients had an intermediate karyotype (azacitidine, 69%; CCR, 74%). All patients had ≥ one blood cytopenia, and 94% had marrow multilineage dysplasia. The median number of azacitidine cycles was eight (range, one to 39 cycles), with a median cycle length of 34 days (range, 15 to 79 days). For the CCR group, the median number of LDAC cycles was 5.5 (range, one to 14 cycles), with a median cycle length of 35 days (range, 15 to 77 days), and the median number of IC cycles was 2.5 (range, one to three cycles). Median duration of BSC was 6 months (range, 2 to 19 months). Among patients who received CCR during the study, 13 received alternative active therapy after withdrawal from the study as follows: patients who received BSC during the study received LDAC (n = 1), IC (n = 5), and azacitidine (n = 2); patients who received LDAC during the study received IC (n = 1) and azacitidine (n = 2); and patients who received IC during the study received LDAC (n = 1) and azacitidine (n = 1). Of patients who received azacitidine during the study, three received LDAC and six received IC after withdrawal from the study.

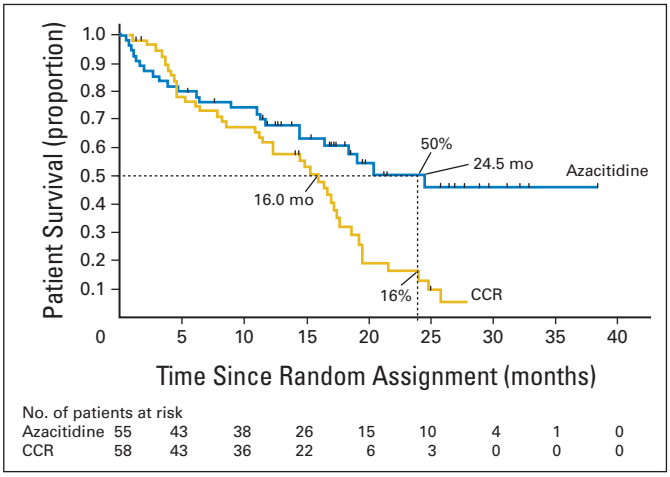

Fig 2. Kaplan-Meier plot of overall survival in patients receiving azacitidine (n = 55) or conventional care regimens (CCR; n = 58). Although the flat part of the curve between 20 and 24 months appears unstable, a consistent effect was observed through these time points with a significantly higher overall survival rate in the azacitidine group versus the CCR group at month 20 (54.1% [95% CI, 38.1% to 67.5%] *v* 19.1% [95% CI, 8.4% to 33.2%], respectively; difference = 34.9% [95% CI, 15.2% to 54.6%]; $P = .0005$), month 24 (50.2% [95% CI, 33.8% to 64.5%] *v* 15.9% [95% CI, 6.2% to 29.7%], respectively; difference = 34.3% [95% CI, 14.4% to 54.1%]; $P = .0007$), and month 27 (45.6% [95% CI, 28.7% to 61.1%] *v* 4.8% [95% CI, 0.5% to 17.9%]; difference = 40.8% [95% CI, 22.3% to 59.4%]; $P < .0001$).

Survival

After a median follow-up time of 20.1 months (range, 0.03 to 38.4 months) in all patients, OS was significantly longer in the azacitidine group compared with CCR (median OS, 24.5 months; 95% CI, 14.6 months to not reached; *v* 16.0 months; 95% CI, 11.5 to 17.5 months, respectively; HR = 0.47; 95% CI, 0.28 to 0.79; $P = .005$; Table 2; Fig 2). The 2-year OS rate was 50% in the azacitidine group versus 16% in the CCR group ($P = .001$).

Results from the preselection analysis showed a significant difference in OS favoring azacitidine (n = 36) versus BSC (n = 27), with median OS of 19.1 *v* 13.4 months, respectively (HR = 0.48; 95% CI, 0.24 to 0.94; $P = .03$). No significant difference was observed for azacitidine (n = 14) versus LDAC (n = 20), with median OS of 24.5 *v* 17.0 months, respectively (HR = 0.37; 95% CI, 0.12 to 1.13; $P = .08$). Median OS was not reached for azacitidine (n = 5) compared with 14.2 months for IC (n = 11). No evidence of statistical heterogeneity of therapeutic benefit between the CCR regimens was observed for OS ($P = .43$). For patients who were considered unfit for IC (ie, patients preselected for BSC or LDAC), OS was significantly longer with azacitidine (n = 50) versus CCR (n = 47; median OS, 24.5 *v* 16.4 months, respectively; HR = 0.44; 95% CI, 0.25 to 0.77; $P = .004$), and the 2-year OS rate was significantly higher for azacitidine-treated patients (51% *v* 13%, respectively; $P = .0003$).

In patients with intermediate-risk cytogenetics, OS was significantly longer in the azacitidine group (n = 38) versus the CCR group (n = 43; median OS, not reached *v* 17.0 months, respectively; HR = 0.47; 95% CI, 0.24 to 0.91; $P = .02$), and the 2-year OS rate was higher for the azacitidine group (53% *v* 23%, respectively; $P = .02$).

Table 2. OS Comparison for Azacitidine *v* CCR in All Patients and According to Investigator Preselection

	All Patients			Azacitidine *v* BSC Only			Azacitidine *v* LDAC			Azacitidine *v* Intensive Chemotherapy		
OS Measure	Azacitidine (n = 55)	CCR (n = 58)	*P*	Azacitidine (n = 36)	BSC Only (n = 27)	*P*	Azacitidine (n = 14)	LDAC (n = 20)	*P*	Azacitidine (n = 5)	Intensive Chemotherapy (n = 11)	*P*
OS, months			.005			.03			.08			.97
Median	24.5	16.0		19.1	13.4		24.5	17.0		NR	14.2	
95% CI	14.6 to NR	11.5 to 17.5		11.2 to NR	5.2 to 17.5		18.4 to NR	14.5 to 25.8		2.7 to NR	10.8 to 24.1	
HR for OS	0.47			0.48			0.37			0.97		
95% CI	0.28 to 0.79			0.24 to 0.94			0.12 to 1.13			0.19 to 5.10		
2-year OS rate, %	50.2	15.9	.001	46.3	0	< .0001	56.3	31.8	.29	60.0	25.0	.19
95% CI	33.8 to 64.5	6.2 to 29.7		27.7 to 63.0			16.4 to 83.3	9.4 to 57.5		12.6 to 88.2	4.1 to 54.8	

Abbreviations: OS, overall survival; CCR, conventional care regimen; BSC, best supportive care; LDAC, low-dose cytarabine; NR, not reached; HR, hazard ratio.

Table 3. Most Common Grade 3 or 4 Hematologic Adverse Events Determined by Laboratory Values Occurring in Patients Receiving Azacitidine or CCR in the Overall Safety Population, by Treatment Group and Investigator Preselection

	All Patients (n = 106)				BSC Only (n = 59)				LDAC (n = 32)				Intensive Chemotherapy (n = 15)			
	Azacitidine (n = 53)		CCR (n = 53)		Azacitidine (n = 34)		BSC Only (n = 25)		Azacitidine (n = 14)		LDAC (n = 18)		Azacitidine (n = 5)		Intensive Chemotherapy (n = 10)	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Thrombocytopenia	48	90.6	44	83.0	31	91.2	17	68.0	13	92.9	18	100	4	80.0	9	90.0
Neutropenia	50	94.3	44	83.0	33	97.1	19	76.0	12	85.7	16	88.9	5	100	9	90.0
Anemia	30	56.6	36	67.9	18	52.9	18	72.0	10	71.4	14	77.8	2	40.0	4	40.0

Abbreviations: CCR, conventional care regimen; BSC, best supportive care; LDAC, low-dose cytarabine.

Within a subset of patients with intermediate-risk cytogenetics with normal karyotypes, OS was similar between azacitidine (n = 19; median OS, 19.1 months) and CCR (n = 33; median OS, 19.5 months; HR = 0.95; 95% CI, 0.41 to 2.16; $P = .89$); the 2-year OS rates were 38% *v* 33%, respectively ($P = .78$). In patients with unfavorable cytogenetics, median OS in the azacitidine (n = 14) and CCR (n = 13) groups was 12.3 and 5.3 months, respectively (HR = 0.66; 95% CI, 0.26 to 1.68; $P = .38$), whereas the 2-year OS rate was 38% for azacitidine, with no patients surviving more than 20 months in the CCR group ($P = .01$).

Response Rates

The morphologic CR rate was 18% (10 of 55 patients) in the azacitidine group and 16% (nine of 58 patients) in the CCR group ($P = .80$). Morphologic CR was reported in three (15%) of 20 patients treated with LDAC, six (55%) of 11 patients treated with IC, and no patients treated with BSC. CR was not achieved in the three patients with CMML.

Transfusion Requirements

Among patients with RBC or platelet transfusion dependence at baseline, a significantly higher proportion achieved transfusion independence with azacitidine compared with CCR for RBC (41% *v* 18%, respectively; $P = .04$) but not for platelets (53% *v* 40%, respectively; $P = .69$); when patients preselected for IC were removed from the analysis, the respective rates for RBC transfusion independence were 44% *v* 15%, respectively ($P = .01$), and the rates for platelets were 50% *v* 40%, respectively ($P = .70$). In the investigator preselection analysis, only the comparison between azacitidine and LDAC for RBC transfusion independence was significant (seven of 10 patients *v* two of 12 patients, respectively, achieving transfusion independence; $P = .03$). The comparison between azacitidine and IC was not possible as a result of low patient numbers.

Adverse Events

Two azacitidine-treated patients and five CCR-treated patients withdrew from the trial without receiving treatment and were not included in the safety analysis. Thus, the safety population included 53 patients in each group, with 25 (47%) of 53 patients assigned to BSC, 18 (34%) of 53 assigned to LDAC, and 10 (19%) of 53 assigned to IC in the CCR group. The most common grade 3 or 4 hematologic adverse events (determined by laboratory values) were thrombocytopenia, neutropenia, and anemia (Table 3). In the overall study population, seven patients discontinued treatment as a result of adverse events, including four patients (7.3%) and three patients (5.2%) in the azacitidine and CCR groups, respectively.

Patients in the azacitidine group had a lower rate of fever requiring intravenous antibiotics compared with the CCR group (0.6 *v* 1.1 instances per patient-year, respectively; relative risk [RR] = 0.51; 95% CI, 0.29 to 0.78; $P = .003$). When patients preselected for IC were removed from the analysis, the RR was no longer significant (0.5 *v* 0.7 instances per patient-year, respectively; RR = 0.68; 95% CI, 0.35 to 1.24; $P = .18$). In the investigator preselection analysis, the difference in antibiotic use was only significant for azacitidine versus LDAC (0.2 *v* 0.8 instances per patient-year, respectively; RR = 0.21; 95% CI, 0.05 to 0.92; $P = .04$).

Azacitidine-treated patients had fewer hospital admissions compared with CCR-treated patients (3.4 *v* 4.3 admissions per patient-year, respectively; RR = 0.79; 95% CI, 0.62 to 1.00; $P = .05$) and fewer total number of days in hospital (26.0 *v* 50.9 days per patient-year; RR = 0.48; 95% CI, 0.44 to 0.52; $P < .0001$). After removing patients preselected for IC, the number of hospital admissions for azacitidine- versus CCR-treated patients was 2.8 *v* 3.5 admissions per patient-year (RR = 0.80; 95% CI, 0.59 to 1.04; $P = .06$), and the total number of days in hospital was 20.7 *v* 31.6 days per patient-year (RR = 0.65; 95% CI, 0.54 to 0.66; $P < .0001$). Using the investigator preselection analysis, the number of hospitalizations per patient-year did not significantly differ between azacitidine and each of the CCR groups. However, azacitidine-treated patients required significantly fewer days in hospital per patient-year versus patients treated with BSC ($P = .001$), LDAC ($P < .0001$), and IC ($P < .0001$).

DISCUSSION

In this analysis, patients with low BM blast count WHO-defined AML (previously classified as RAEB-t using FAB criteria) clearly benefited from azacitidine treatment compared with CCR, with half of patients in the azacitidine group still alive at 2 years compared with only 16% in the CCR group. These findings confirm previous results from a pooled analysis (three studies) of azacitidine in 27 patients from the Cancer and Leukemia Group B (CALGB) 9221 clinical trial with WHO AML (median OS, 19.3 months).[30]

When treated with BSC only, patients with RAEB-t have a median OS of ≤ 6 months.[29,31-33] In a Düsseldorf MDS registry data update, patients with RAEB-t treated with BSC only (n = 175; median

age, 71 years) had a median OS of 5 months and a 2-year OS rate of 8% (U. Germing, personal communication, March 2009). Among patients treated with IC in the Düsseldorf registry (n = 88), CR was achieved in 64% and 46% of patients younger than 65 and ≥ 65 years, respectively, whereas median OS was 17 months and the 2-year OS rate was 34%, with no significant differences in OS based on age. In another experience in 106 patients with RAEB-t (median age, 59 years) treated with IC, the CR rate was 66%, and the median event-free survival duration was 30 weeks, similar to the results reported in AML patients with BM blasts more than 30% in the same study.[34] Patients in the Düsseldorf registry treated with LDAC had a median OS of 18 months and a 2-year OS rate of 25%. Other studies of LDAC have reported median OS durations of ≤ 17 months.[35,36] Also, in patients with RAEB-t treated with tipifarnib, the median OS was only 9.2 months.[37]

It should be considered whether the patients with AML analyzed in the present study (ie, AML with 21% to 30% BM blasts) are representative of patients with AML as a whole or whether they carry a better prognosis than patients with AML with higher BM blast percentages. Controversy remains concerning whether the natural history and responsiveness to therapy of patients with BM blasts of 20% to 30% more closely resembles that of untreated AML[31,38] or advanced MDS.[39,40] Several studies show no difference in OS between patients with BM blasts of 20% to 30% versus patients with BM blasts more than 30%, including patients treated with IC.[34,41,42] Therefore, caution is required when comparing results from the present trial with those from broad groups of elderly patients with AML, in whom blast percentages are higher. However, the 2-year OS rate (50%) observed with azacitidine in low BM blast count (20% to 30%) AML seems higher than that reported previously in elderly patients with AML, irrespective of treatment received. Indeed, although CR rates of up to 60% have been reported in elderly patients with AML treated with IC, median OS ranged from 7 to 12 months, with 2-year OS rates of 10% to 27%.[10,11,17-19,43,44] Moreover, IC is often contraindicated in elderly patients with AML, irrespective of BM blast percentage, and is generally administered to only 30% to 60% of these patients.[13] Few treatment options are available for patients who cannot receive IC, and many patients still receive palliative BSC.[7,13] In our study, we found that azacitidine significantly improved survival and significantly reduced time spent in hospital compared with BSC. Although LDAC significantly improved survival compared with hydroxyurea in a randomized study in elderly patients with AML, it yielded a median survival time of only 4 months and a 2-year OS rate of less than 10%.[45] Similar results have been reported in other series of elderly patients with AML treated with LDAC, with a median OS of ≤ 11 months[17,46,47] and a 2-year OS rate of 15%.[17] We found significantly better survival with azacitidine versus CCR in patients considered unfit for IC, who represented the majority (86%) of our patients.

With regard to newer treatments under evaluation in elderly patients with AML, tipifarnib failed to demonstrate any survival benefit over BSC.[16] Clofarabine[15,48] and cloretazine[49] have reported median OS of 5 to 5.8 months, and 3.1 months, respectively, and 1-year OS rates of approximately 25% and 14%, respectively. Furthermore, both agents are associated with substantial myelosuppression,[15,49,50] and clofarabine is associated with acute renal failure in up to 19% of patients.[15]

The survival benefit obtained with azacitidine, despite a low CR rate (18%), suggests that azacitidine can prolong survival in the absence of a CR, a finding similar to that seen in patients with intermediate-2– and high-risk MDS in the original study population.[20] Significantly more azacitidine-treated patients achieved RBC transfusion independence and azacitidine significantly reduced the number of days in hospital compared with CCR, even when excluding patients preselected for IC. These are important azacitidine-associated benefits in elderly patients in whom treatment options that reduce morbidity and the need for hospitalization are preferred.

In conclusion, azacitidine prolongs survival and is well tolerated when compared with conventional and low-dose induction chemotherapy in older adult patients with WHO-defined AML with low BM blast counts (20% to 30%). The activity of azacitidine in AML with greater degrees of BM infiltration (> 30% BM blasts) is currently under investigation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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