Published in final edited form as:
Crit Rev Oncol Hematol. 2010 December ; 76(3): 218–227. doi:10.1016/j.critrevonc.2010.04.005.

Effects of azacitidine compared with conventional care regimens in elderly (≥75 years) patients with higher-risk myelodysplastic syndromes☆

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Abstract

This analysis compared azacitidine (AZA) to conventional care regimens (CCR) and their associated overall survival (OS) and tolerability in the subset of 87 elderly (≥75 years) patients with higher-risk MDS (FAB: RAEB, RAEB-t, CMML and IPSS: Int-2 or High) from the AZA-001 trial. Patients were randomized to AZA (75 mg/m^2/day subcutaneously×7 days every 28 days) (n = 38) or CCR (n = 49) and had median ages of 78 and 77 years, respectively. AZA significantly improved OS vs CCR (HR: 0.48 [95%CI: 0.26, 0.89]; p = 0.0193) and 2-year OS rates were 55% vs 15% (p < 0.001), respectively. AZA was generally well tolerated compared with CCR, which was primarily best supportive care (67%). Grade 3–4 anemia, neutropenia, and thrombocytopenia with AZA vs CCR were 13% vs 4%, 61% vs 17%, and 50% vs 30%, respectively. Given this efficacy and tolerability, AZA should be considered the treatment of choice in patients aged ≥75 years with good performance status and higher-risk MDS.

☆This study is registered with ClinicalTrials.gov, number NCT00071799.

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Keywords

Azacitidine; Low-dose ara-C; Elderly; Myelodysplastic syndromes; MDS; Acute myeloid leukemia; AML; Survival

1. Introduction

Myelodysplastic syndromes (MDS) are common and prevalent hematologic disorders. The estimated annual incidence of MDS in North American and European populations is approximately 3.3–4.5 cases per 100,000 [1]. However, the incidence increases with age, and over the age of 70, the annual incidence of MDS is as high as 15–50 cases per 100,000/year [2]. MDS is associated with impaired quality-of-life, and severe cytopenias can lead to potentially fatal bleeding or infections [3]. Patients with more advanced MDS subtypes are at high risk of progression to acute myeloid leukemia (AML), and unless patients are able to receive allogeneic stem cell transplant, or have competing comorbidities, MDS is their most likely cause of death [4–6].

Treatment options for elderly patients with MDS are very limited, and many factors increase the likelihood that they will not receive any active MDS treatment. These include the presence of age-related comorbidities and functional impairment, poor tolerability and/or ineffectiveness of available cytotoxic therapies, and patient preferences combined with physician reluctance. Results of a large cross-sectional survey of physicians treating older patients with MDS (most patients were >70 years of age) indicated that 27% of newly diagnosed patients with higher-risk disease and 24–49% of patients with established higher-risk MDS received supportive care only [7]. Moreover, unlike experience in younger patients with MDS, when elderly patients do receive active treatment, there is little evidence for any improvement in survival [8].

The most commonly applied treatments for patients with MDS are hypomethylating agents, intensive chemotherapy, low-intensity cytotoxic regimens, or palliative care, and it is difficult to determine which treatment approach may benefit elderly patients most [3]. There is a paucity of clinical trials in elderly patients and a general lack of data regarding outcomes of cytotoxic therapy for older patients with higher-risk MDS [9]. Even the definition of “elderly” varies widely, with patients over age 60, 65, or 70 years of age considered “elderly” in published studies [10–12]. In the absence of clear guiding data, clinical decisions may be extrapolated from data in older patients with AML [12], as it has been suggested that in older patients, higher-risk MDS and AML are two points on the biological continuum of the same disease [2]. Many patients who meet the FAB classification for RAEB-t also meet the WHO classification for AML (≥20% marrow blasts) [13]. Moreover, higher-risk MDS and AML have comparable prognoses and treatment is often similar [3].

The international multicenter randomized phase III AZA- 001 trial established that the demethylating agent, azacitidine, significantly improves overall survival (OS) in patients with higher-risk MDS, including patients whose disease meets the definition of WHO-AML (20–30% marrow blasts) [14]. Patients in the AZA-001 trial tended to be older, with a median age of 69 years (range 38–88). Approximately one quarter of all randomized patients

were ≥75 years or age. To further explore toxicity and outcomes in elderly patients with higher-risk MDS or AML with 20–30% marrow blasts, these analyses were performed for the prospectively defined subgroup of patients in AZA-001 who were ≥75 years of age at entry.

2. Methods

2.1. Patients

Patients aged ≥18 years with higher-risk MDS (FAB-defined refractory anemia with excess blasts [RAEB], RAEB in transformation [RAEB-t], or chronic myelomonocytic leukemia [CMML] with more than 10% marrow blasts and a white blood count $<13\times10^9$/L, and an IPSS risk of Intermediate-2 or High [5]) were eligible. Patients must have had an ECOG performance status of 0–2 and an estimated life expectancy of ≥3 months. Patients with therapy-related MDS, prior azacitidine treatment, or who were planned to undergo allogeneic stem cell transplantation were excluded.

For this subgroup analysis, all patients aged ≥75 years were evaluated for efficacy (intention-to-treat), and all patients who received at least 1 dose of study drug and had at least 1 post-baseline assessment were evaluated for safety.

2.2. Study design

As previously reported, AZA-001 was a phase III, international, multicenter, randomized, controlled, parallel-group study [14]. All patients provided written, informed consent before participation. Study enrollment and monitoring were conducted by site investigators and central pathology reviewers, with standardized central review of cytogenetic data.

Before randomization, investigators preselected each patient to receive what they considered to be the most appropriate of 3 protocol-specified conventional care regimens (CCR), based on clinical status, age, ECOG performance status, and comorbidities. Subsequently, patients were randomized to either azacitidine or CCR. If randomized to azacitidine, pts received it (regardless of their preselected treatment) at 75 mg/m^2/day subcutaneously×7 days every 28 days for a minimum of 6 cycles. If randomized to CCR, pts received their preselected treatment. The 3 CCR regimens were: (1) best supportive care (BSC), which included blood product transfusions, antibiotics, and G-CSF for neutropenic infection (but not prophylaxis); (2) low-dose ara-C (LDAC) 20 mg/m^2/day subcutaneously×14 days every 28 days (delayed until blood count recovery) for a minimum of 4 cycles; or (3) intensive chemotherapy, which comprised induction with ara-C 100–200 mg/m^2/day by continuous IV infusion for 7 days + 3 days of IV daunorubicin (45–60 mg/m^2/day), idarubicin (9–12 mg/m^2/day), or mitox-zantrone (8–12 mg/m^2/day). All patients in the study could receive BSC.

Per protocol, azacitidine dosing cycles could be delayed and/or modified due to hematologic toxicity by 7–14 days, as needed, until hematologic recovery. For patients with baseline counts of WBC $\geq3\times10^9$/L and ANC $\geq1.5\times10^9$/L and platelets $\geq75\times10^9$/L, dose modification or delay could occur if the absolute neutrophil count (ANC) nadir was $\leq1\times10^9$/L and/or platelet nadir was $<50\times10^9$/L. For patients with baseline counts of WBC $<3\times10^9$/L or ANC

<1.5×10^9/L or platelets <75×10^9/L, dose modification or delay could occur ifWBCor ANC or platelet nadir decreased ≥50% from baseline.

Azacitidine and CCR were continued until study end (12 months after the last patient was randomized) or patient discontinuation due to unacceptable toxicity or disease progression, as defined per International Working Group (IWG) 2000 criteria for MDS [15]. Patients could not receive erythropoietic stimulating agents while on study.

2.3. Assessment of efficacy and safety

Efficacy comparisons were made between the azacitidine and CCR treatment groups. The primary efficacy endpoint was OS. Secondary efficacy endpoints included hematologic response (complete [CR] and partial remission [PR]) and hematologic improvement (HI) assessed using IWG 2000 criteria for MDS [15], and red blood cell (RBC) transfusion independence (TI) in patients with RBC transfusion-dependence at baseline. To be considered baseline RBC transfusion-dependent, patients had received at least 1 transfusion during the 56-day pre-baseline period prior to randomization. TI during treatment was defined as a transfusion-free period of ≥56 consecutive days.

All patients who received at least 1 dose of study drug and had at least 1 safety assessment comprised the safety-evaluable population. Safety results are shown for the azacitidine and total CCR cohorts and are also presented by preselection to treatment (Fig. 1). That is, results are reported for the group of patients who were preselected to BSC (*N*= 60) then randomized to azacitidine or BSC, and for the group of patients preselected to receive LDAC (*n* = 24) then randomized to azacitidine or LDAC. Three patients were preselected for intensive chemotherapy, 1 was randomized to azacitidine treatment and 2 to CCR treatment. Of the latter, only 1 patient actually received intensive chemotherapy. Adverse events for this patient are reported descriptively and not presented in data tables. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria, version 2.0.

Rates of hospitalization due to adverse events in the azacitidine and CCR groups were calculated as the number of hospitalizations per patient-year of drug exposure and were assessed at 6 months and over the course of the study.

2.4. Statistical methods

These analyses were performed for the subgroup of patients ≥75 years of age, as prospectively defined in the AZA-001 statistical analysis plan. Randomization and analyses were stratified by FAB subtype and IPSS risk group. OS was defined as the time from randomization until death from any cause. Surviving patients were censored at last follow-up. OS curves and estimated survival at 2 years were generated using Kaplan–Meier methods and compared using stratified log-rank tests. For the primary analysis comparing OS between the azacitidine and CCR, a Cox proportional hazards regression model was used, stratified by FAB and IPSS with a factor for treatment, to estimate hazard ratios (HR) and associated 95% confidence intervals (CI). To adjust for baseline imbalances, ECOG status, LDH, number of RBC transfusions, Hgb, and presence or absence of −7/del(7q) at

baseline were added as covariates to the final model in addition to treatment, FAB, and IPSS.

In the final model, ECOG performance status, LDH, number of RBC transfusions, hemoglobin (Hgb), and presence or absence of −7/del(7q) at baseline were included as covariates. Response (CR, PR, TI, and HI) rates with azacitidine and CCR were compared using Fisher's exact test.

Adverse events are presented descriptively by overall frequency and by frequency per blocks of 2 cycles (1–2, 3–4, 5–6). Additionally, adverse event rates were calculated as events per patient-year of exposure. Exposure was calculated from the date of the first dose until 42 days after the last dose of azacitidine or LDAC; from randomization to last study visit for BSC; and from first dose to 70 days after last dose for intensive chemotherapy. The relative risk (RR) of hospitalization due to adverse events was computed as the ratio of azacitidine to CCR.

3. Results

3.1. Patient disposition

Eighty-seven patients in the AZA-001 study were ≥75 years of age at entry and comprise the intent-to-treat (ITT) population for this analysis. The median age of this subgroup was 78 years (range 75–88) and mean time (±SD) from diagnosis was 1.0±1.7 years. Thirty-eight patients were randomized to azacitidine and 49 to CCR, with the difference in numbers due to the fact that initial randomization was not stratified by age. Two patients (1 randomized to BSC and 1 to intensive chemotherapy) did not receive any treatment before withdrawing from the trial and are excluded from safety analyses.

Patients in the azacitidine and CCR groups had comparable baseline characteristics (Table 1). Most patients were ECOG performance status 0–1 and were RBC transfusion-dependent at baseline. Thirty patients (35%) met the criterion for WHO-AML (20–30% blasts). Prior to randomization, the majority of these elderly patients were preselected to receive BSC(60/87, 69%) (Fig. 1). In patients randomized to the CCR arm (n = 49), 33 (67%) were preselected to BSC, 14 (29%) to LDAC, and only 2 (4%) to intensive chemotherapy. Of the 38 patients who were randomized to, and received azacitidine, 27 (71%) had been preselected for BSC, 10 (26%) for LDAC, and 1 (3%) for intensive chemotherapy. Patient comorbidities and relevant medical histories are shown in Table 2.

3.2. Efficacy

The median number of azacitidine cycles received was 7.5 (range 1–23) and median number of LDAC cycles received was 5.0 (range 1–13). Median azacitidine treatment cycle length was 28.0 days (21–106) and median LDAC treatment cycle length was 32.0 days (27–65). Of all 299 azacitidine cycles administered, 51% of cycle lengths were ≤28 days, 26% were between 29 and 35 days, and 23% were greater than 35 days. Of the 64 administered LDAC doses, 39% of cycle lengths were ≤28 days, 41% were between 29 and 35 days, and 20% were greater than 35 days.

Treatment with azacitidine was associated with a statistically significant improvement in OS compared with CCR. With a median follow-up of 17.7 months, the median OS in the azacitidine group was not reached [95%CI: 11.2, not reached] and median OS in the CCR arm was 10.8 months [95%CI: 7.3, 17.5]. The unadjusted HR was 0.57 [95%CI: 0.31, 1.06; $p = 0.074$]; however, after adjusting for baseline imbalances between treatment groups, the HR was 0.48 [95%CI: 0.26, 0.89], log-rank $p = 0.0193$ (Fig. 2). At 2 years, the proportion of patients still alive was significantly higher in the azacitidine group compared with the CCR group: 55% vs 15%, respectively ($p < 0.001$).

Forty-three percent (10/23) of patients with baseline RBC transfusion-dependence in the azacitidine group achieved RBC TI, vs 22% of patients in the combined CCR group ($p = 0.14$). In the azacitidine and combined CCR groups, 58% vs 39%, respectively ($p = 0.09$) achieved HI (major + minor) (Fig. 3).

3.3. Safety

Azacitidine was generally well tolerated compared with CCR, for which BSC was the predominant treatment approach (67%). Two patients receiving azacitidine had dose reductions (1 patient to 25 mg/m^2 and 1 patient to 37.5 mg/m^2). Table 3 shows Grade 3–4 adverse events of interest by cycle for the azacitidine and CCR cohorts and also for the preselection cohorts. The frequency of adverse events reported for azacitidine-treated patients decreased after the first 2 cycles. Table 4 shows the most frequent Grade 3–4 adverse events over the entire study. Only 1 patient received intensive chemotherapy and Grade 3 or 4 adverse events for this patient included thrombocytopenia, neutropenia, atrial fibrillation, myocardial infarction, catheter-site hemorrhage, neutropenic sepsis, dizziness, and dyspnea. Because there is only 1 patient receiving intensive chemotherapy, these data are excluded from safety tables.

Overall, 11/38 (29%) patients randomized to azacitidine and 29/49 (59%) patients randomized to CCR discontinued before study end. Of them, 1 azacitidine (3%) and 7 CCR patients (14%) discontinued due to disease progression. Discontinuations due to adverse events occurred in 5 patients (13%) who received azacitidine; for 2 patients, the adverse events were considered to be related to treatment (febrile neutropenia and bronchopulmonary aspergillosis with septic shock). Four patients (8%) who received CCR discontinued due to adverse events, including 1 patient who received LDAC who discontinued due to thrombocytopenia, which was considered treatment related. Early “induction” deaths (i.e., within 90 days of randomization to treatment) occurred for 6 patients who received azacitidine, 1 who received BSC, and 2 who received LDAC. Three deaths in the azacitidine arm were considered possibly related to treatment (respiratory infection in a patient with COPD, hematemesis, and sepsis) and 1 death in the LDAC armwas considered possibly related to treatment (stroke).

Cytopenias occurred most frequently in early treatment cycles. Fig. 4 shows Hgb, platelet, and neutrophil nadir counts over the course of the study for the azacitidine and CCR cohorts and for preselection-defined cohorts. There was a trend for increased nadir values for Hgb and platelets after the first few treatment cycles for azacitidine-treated patients, although ANC nadir values with azacitidine remained low. Mean numbers of RBC transfusions over

the course of the study were slightly lower with azacitidine than with BSC and were consistently lower than with LDAC. Relatively few infections were reported in these patients and number of infections (any grade) tended to decrease after the first 2 cycles (Table 5) of treatment in both treatment groups.

At 6 months, the rate of hospitalization due to adverse events was 3.07 per patient-year of exposure with azacitidine and 2.94 per patient-year with CCR[RR = 1.00, 95%CI: 0.69, 1.47] Hospitalizations due to adverse events over the course of the entire study in the azacitidine group decreased from the 6-month rate to 2.40 per patient-year, whereas, rate in the CCR group remained approximately the same at 2.90 per patient-year [RR = 0.81, 95%CI: 0.59, 1.11]

No clinically relevant differences in treatment-related adverse events with azacitidine were observed between patients age ≥75 years and patients age <75 years (data not shown).

4. Discussion

Azacitidine significantly improved OS compared with the most commonly used conventional care regimens in these elderly (≥75 years) patients with higher-risk MDS, approximately one-third of whom also fulfilled criteria for WHO-defined AML (20–30% blasts). At a median follow-up of 17.7 months, the median OS in the azacitidine group was not reached, and the proportion of patients who received azacitidine and were alive at 2 years (55%) was more than threefold that of the CCR cohort (15%). This is an extremely promising finding in this population of elderly patients with higher-risk MDS, particularly when compared with other controlled clinical studies. In a comprehensive literature review by Deschler et al. of active treatment trials conducted between 1989 and 2006 that included 40 or more patients >60 years of age with higher-risk MDS or AML, median OS ranged from approximately 7 months to less than 2 years [2].

Therapeutic choices, which range from palliative care to intensive disease-directed chemotherapy treatments, involve a number of considerations for any patient with MDS, but comorbidities and performance status are particularly important factors when choosing treatment for elderly patients. The majority of elderly patients in this analysis had been preselected to receive only BSC before randomization, suggesting that clinicians were reluctant to prescribe active disease-directed chemotherapy. Indeed, some consensus guidelines recommend only palliative care in patients aged≥75, regardless of clinical status [16]. However, age should not be the most important determinant in deciding whether patients receive treatment that may alter the natural history of the disease. In the study by Greenberg et al., untreated patients over 70 years of age with MDS classified as IPSS Int-2 and High who received only BSC had median OS of approximately 1.2 years and 0.4 years, respectively [5]. Patients in our current analysis, who were older on average than those in the Greenberg study and who received active treatment with azacitidine had much better survival: at 2 years, 55% of patients who received azacitidine, with median age of 78 years, remained alive.

Age of 75 years or older is an independent poor prognostic factor associated with higher mortality in patients who receive intensive chemotherapy, which is usually reserved only for the fittest elderly patients. In a retrospective analysis of 998 patients of median age 71 years (range 65–89) with high-risk MDS or AML receiving intensive chemotherapy, induction mortality was 29% [12]. In the current analysis, only 3 patients (8%) receiving azacitidine died during the first 90 days after randomization due to causes thought to be related to study treatment. Too few patients received intensive chemotherapy in this elderly subgroup to assess treatment effects on OS.

The other active CCR in this study was LDAC. In controlled trials, LDAC has not shown a survival advantage compared with BSC in MDS [17,18], although a recent study by Burnett et al. showed an OS benefit in LDAC-treated older patients (median age 74 years) with AML and higher-risk MDS who achieved CR, compared with hydroxyurea [8]. In the Burnett study, survival with LDAC was strongly associated with response: median OS was 80 weeks in patients receiving LDAC who achieved CR vs 18 weeks in patients who did not achieve CR. Notably, CR is not a prerequisite for prolonged OS in patients receiving azacitidine [19]. In patients of any age, LDAC has a substantial risk of toxicity, causing death from hypoplasia due to infections or hemorrhage in 10% to 24% of cases in some series [17,20,21]. In the study by Burnett et al. above, induction death occurred in 26% of patients [8].

The primary reason many elderly patients do not receive active therapy is high treatment-related morbidity and mortality. Azacitidine was generally well tolerated in this elderly population, with 77% of patients receiving azacitidine in 4–5-week cycles and only 4% of patients requiring dose reductions. There did not appear to be any clinically relevant differences in reported adverse events with azacitidine between this cohort of patients and study patients <75 years of age. As reported in other studies [22–24], the majority of treatment-related adverse events with azacitidine, including cytopenias, occurred during early treatment cycles and decreased in frequency with continued dosing. Consistent with this finding, nadir hematology values increased and transfusion requirements decreased with continued azacitidine dosing. Additionally, rates of infection with azacitidine in this analysis were not different from rates in the CCR groups and also tended to decrease over time. Accordingly, hospitalization rates with azacitidine were higher in the first 6 months of the study, then declined, for a lower overall rate over the entire study period. In contrast, hospitalization rates with CCR were comparable to those with azacitidine at 6 months but did not decline over the course of the study overall. Adverse events that typically occur during azacitidine administration, such as injection site reactions and gastrointestinal events, were not usually serious and were managed with corticosteroids and antihistamines, or laxatives and antiemetics, respectively. Moreover, hematologic adverse events with azacitidine may be managed by dose reductions or delays, use of concomitant medications, or transfusions [24].

Age alone should not be considered a definitive indicator of functional decline. For elderly patients with MDS or AML, advanced age should not preclude the consideration of effective treatments, such as azacitidine, which has been shown to alter the natural history of the disease [25]. As with any prospective clinical trial, there is a degree of uncertainty as to the

ability to generalize outcomes from a study cohort to a population-based unselected cohort. The results of this subanalysis augment the few available data regarding active treatment outcomes in elderly patients (≥75 years) with higher-risk MDS or AML with 20–30% blasts, and show azacitidine can significantly prolong survival and is generally well tolerated in these patients with a good performance status.

Acknowledgments

The study was funded by Celgene Corporation. The paper was written by John F. Seymour and other co-authors who had access to all data and controlled all content. Sheila Truten, B.S. and Neil Malone, M.A., provided editorial assistance and Indrasiri Fernando, Ph.D., provided statistical support during manuscript development. ST is employed by MC2, Wynnewood, PA, and was compensated by Celgene Corporation; NM and IF are employed by Celgene Corporation, Summit, NJ.

Conflict of interest statement

John F. Seymour consulted with Celgene, received honoraria and research funding (participation as clinical trial investigator) from Celgene, and participated in advisory board meetings for Celgene. Pierre Fenaux received research funding (participation as clinical trial investigator) from Celgene, Amgen and Roche; received honoraria from Roche, Celgene, Amgen, Cephalon, Merck Sharp and Dohme, GlaxoSmithKline, and Johnson and Johnson. Lewis R. Silverman has received honoraria from Celgene. Ghulam J. Mufti has consulted with Amgen, received research funding (participation as clinical trial investigator) from Celgene, received honoraria from Celgene, and participated in advisory board meetings for Celgene. Eva Hellstrom-Lindberg consulted with Celgene and received research funding (participation as clinical trial investigator) from Celgene. Valeria Santini has received honoraria from Celgene, Novartis, and Johnson and Johnson for lecturing. Alan List has consulted for S*Bio, received research funding (participation as clinical trial investigator) and honoraria from Celgene, and participated in advisory board meetings for Celgene and Aplastic Anemia&MDSMedical. StevenD. Gore consulted with Celgene, received research funding (participation as clinical trial investigator) from Celgene, and is a Celgene stockholder. Jay Backstrom is employed by Celgene and holds Celgene stock and stock options. David McKenzie was employed by Celgene. CL Beach is employed by Celgene and holds Celgene stock and stock options.

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Biography

Professor John Seymour is Head of the Department of Haematology, Peter MacCallum Cancer Centre. Dr. Seymour received his M.B., B.S. degrees from the University of Melbourne in 1987, pursued training in Haematology including a fellowship at the M.D. Anderson Cancer Center in Houston.

Dr. Seymour successfully completed his Ph.D. studies at the Ludwig Institute for Cancer Research. He is a member of several national and international scientific committees including, Cancer Australia Advisory Groups, the Scientific Advisory Committee for the International Workshop on NHL, International Conference on Malignant Lymphoma, and the International Workshop on Myelodysplasia and Board of Directors of the International Extranodal Lymphoma Study Group. He is the current Chairman of the major national clinical trials co-operative group in hematologic malignancies in Australia, the Australasian Leukaemia & Lymphoma Group, and previous board member of the Leukaemia Foundation of Victoria (2000–2005).

He is frequent invited speaker nationally and internationally, member of numerous professional societies, and the Editor-in-Chief of Leukemia and Lymphoma and on the editorial boards of the Journal of Clinical Oncology, British Journal of Haematology, and Leukemia Research. He has also authored 13 book chapters, more than 250 peer-reviewed publications, and approximately 350 conference abstracts. Actively involved in research, Dr. Seymour has received more than $2.5 million dollars of competitive grant funding in the last 5 years and is national study chairman for 13 ongoing national or international clinical trials.

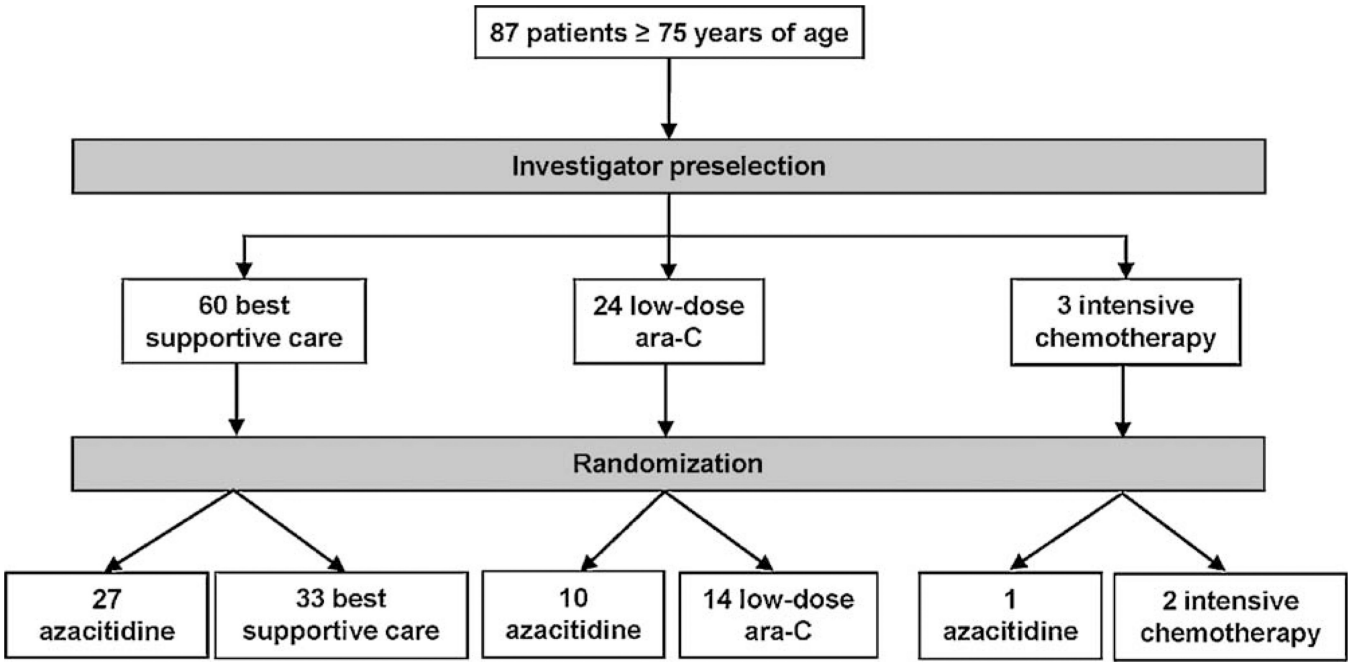

Fig 1.
Patient disposition showing preselection and randomization to treatment.

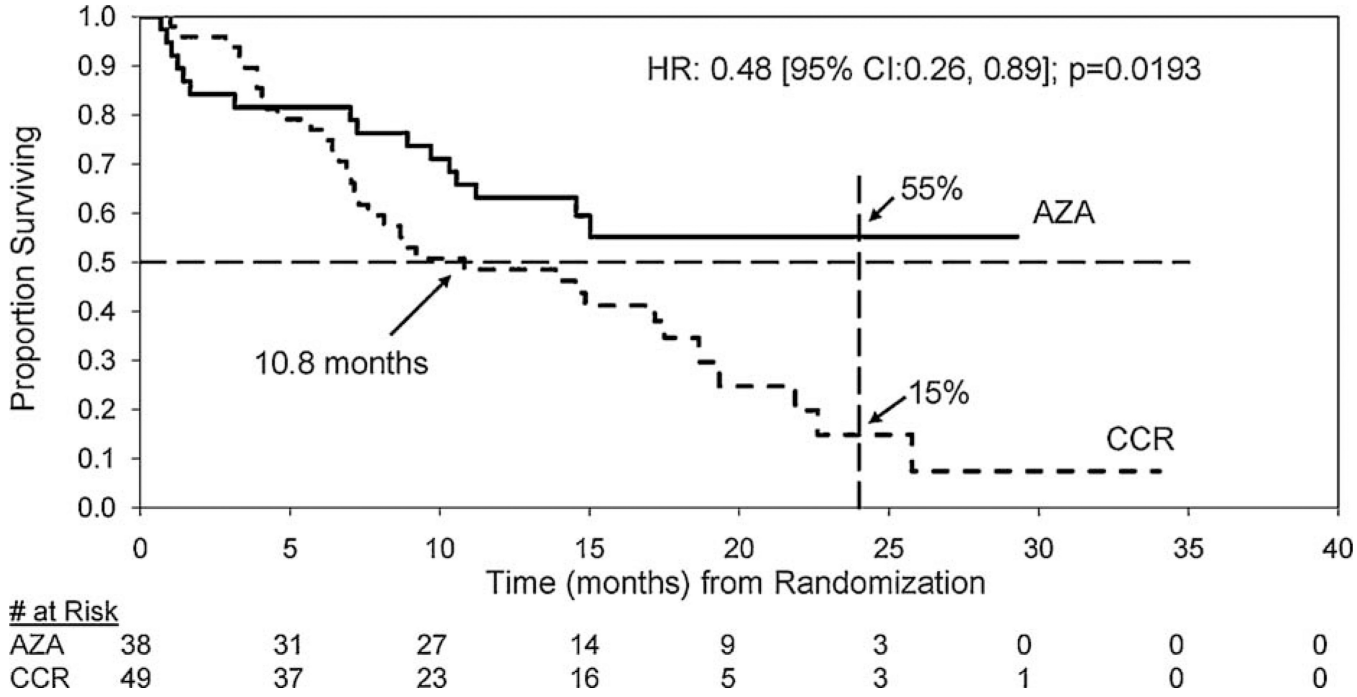

Fig 2.
Overall survival azacitidine (AZA) vs CCR.

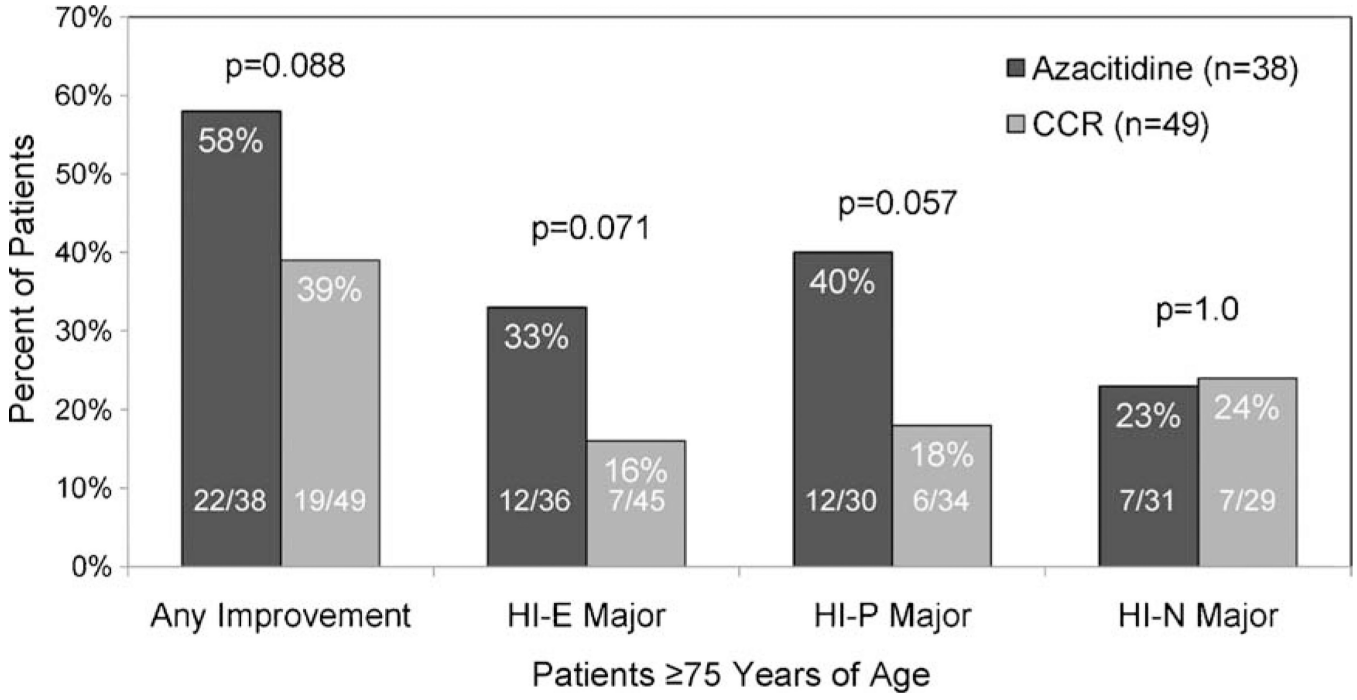

Fig 3.

Hematologic improvement azacitidine vs CCR (HI-E = hematologic improvement in erythroid lineage; HI-P = platelet lineage; HI-N = neutrophil lineage).

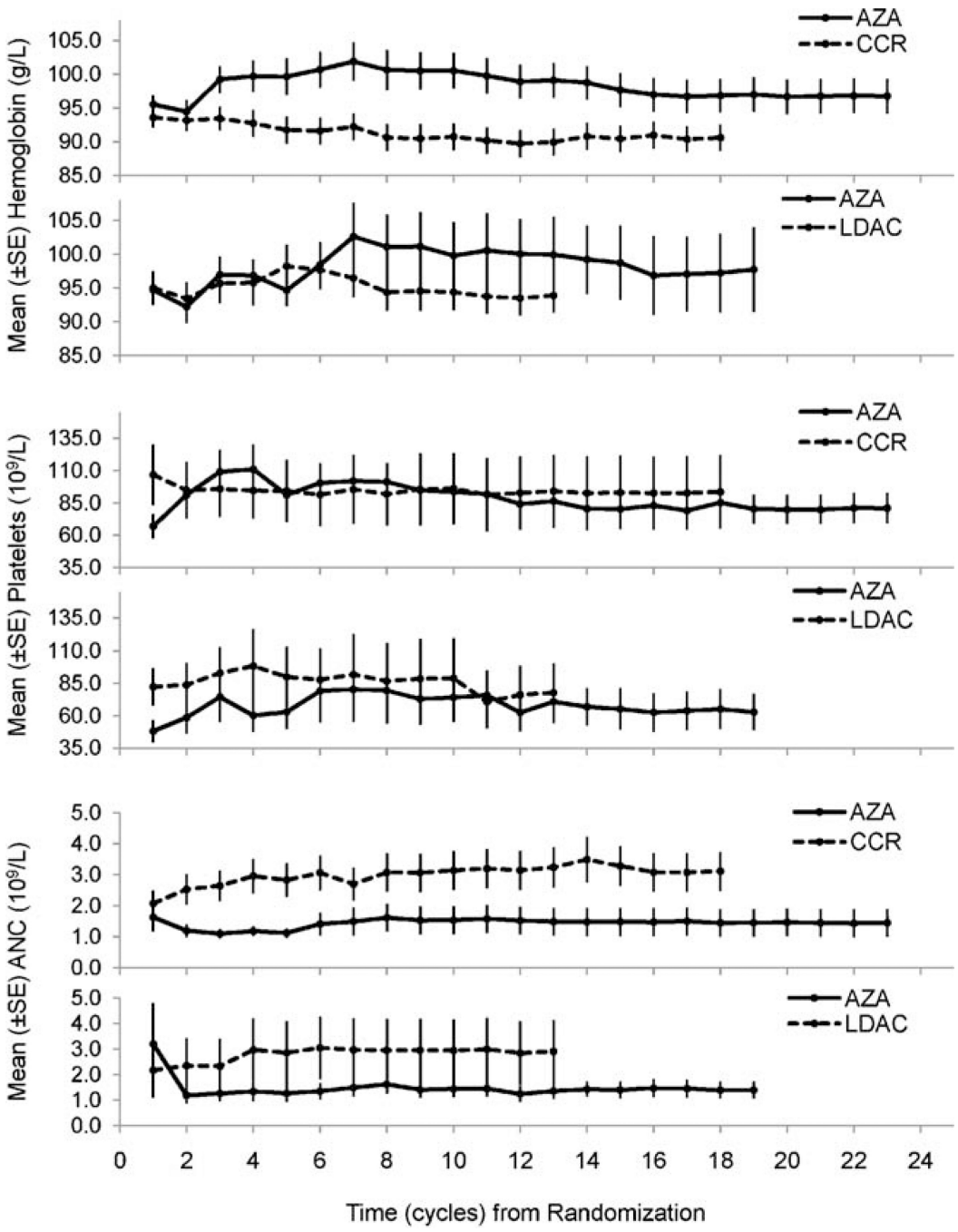

Fig 4.

Nadir Hgb, platelet, and ANC values over time: azacitidine vs CCR and preselection to LDAC comparisons.

Table 1

Demographic and disease characteristics at baseline for the subgroup of patients aged ≥75 years in AZA-001.

	Azacitidine (*n* = 38)	Total CCR (*n* = 49)	CCR by treatment		
			BSC (*n* = 33)	LDAC (*n* = 14)	IC (*n*=2)
Age (years)					
Median (range)	78 (75–83)	77 (75–88)	78 (75–88)	77 (75–85)	76 (75–76)
Gender, *n* (%)					
Male	27 (71)	31 (63)	21 (64)	9 (64)	1 (50)
Time since original diagnosis (years)					
Mean±SD (range)	0.8±1.1 (0–4.0)	1.1±2.0 (0–10.0)	1.3±2.3 (0–10.0)	0.6±1.4 (0–5.0)	1.0±0 (1.0–1.0)
IPSS, *n* (%)					
Intermediate-1	3 (8)	2 (4)	2 (6)	0	0
Intermediate-2	15 (39)	22 (45)	16 (49)	6 (43)	0
High	19 (50)	22 (45)	14 (42)	6 (43)	2 (100)
Indeterminable	0	2 (4)	0	1 (7)	0
Not applicable	1 (3)	1 (2)	1 (3)	1 (7)	0
Cytogenetics, *n* (%)					
Normal	17 (45)	22 (45)	12 (36)	9 (64)	1 (50)
IPSS					
Good	19 (50)	26 (53)	16 (49)	9 (64)	1 (50)
Intermediate	9 (24)	9 (18)	6 (18)	3 (21)	0
Poor	8 (21)	12 (24)	10 (30)	1 (7)	1 (50)
Missing	2 (5)	2 (4)	1 (3)	1 (7)	0
Cytopenias, *n* (%)					
1	0	5 (10)	4 (12)	1 (7)	0
2	12 (32)	22 (45)	16 (48)	5 (36)	1 (50)
3	26 (68)	22 (45)	13 (39)	8 (57)	1 (50)
Bone marrow blasts, *n* (%)					
≥5% and ≤10%	6 (16)	6 (12)	5 (15)	1 (7)	0
>10% and ≤20%	20 (53)	25 (51)	19 (52)	5 (36)	1 (50)
>20% and ≤30%	12 (32)	18 (37)	9 (27)	8 (57)	1 (50)

	Azacitidine (*n* = 38)	Total CCR (*n* = 49)	CCR by treatment		
			BSC (*n* = 33)	LDAC (*n* = 14)	IC (*n*=2)
ECOG status, *n* (%)					
Grade 0	8 (21)	21 (43)	9 (27)	10 (71)	2 (100)
Grade 1	27 (71)	22 (45)	18 (55)	4 (29)	0
Grade 2	3 (8)	6 (12)	6 (18)	0	0
Transfusion dependent, *n* (%)					
RBC	23 (61)	32 (65)	24 (73)	7 (50)	1 (50)
Platelets	10 (26)	8 (16)	4 (12)	4 (29)	0

CCR= conventional care regimens; BSC = best supportive care; LDAC= low-dose ara-C; IC = intensive chemotherapy; ECOG= Eastern Cooperative Oncology Group.

Table 2

Comorbidities/patient history at study entry, *n* (%).

	Azacitidine (*n* = 38)	Total CCR (*n* = 49)	CCR by treatment		
			BSC (*n* = 33)	LDAC (*n* = 14)	IC (*n*=2)
Myocardial infarction	3 (8)	6 (12)	6 (18)	0	0
Angina pectoris	6 (16)	8 (16)	6 (18)	2 (14)	0
Stroke or TIA	2 (5)	1 (2)	1 (3)	0	0
Ventricular arrhythmia	2 (5)	4 (8)	3 (9)	1 (7)	0
Congestive heart failure	1 (3)	7 (14)	4 (12)	3 (21)	0
COPD	6 (16)	6 (12)	6 (18)	0	0
Diabetes mellitus	6 (16)	6 (12)	4 (12)	2 (14)	0
Smoker	18 (47)	16 (33)	11 (33)	4 (29)	1 (50)
Prior MDS treatments[a]	4 (11)	9 (18)	6 (24)	1 (7)	0
Prior radiation, chemotherapy, or cytotoxic therapy for non-MDS conditions	1 (3)	2 (4)	2 (6)	0	0

BSC = best supportive care; LDAC= low-dose ara-C; IC = intensive chemotherapy; CCR= conventional care regimens; MDS= myelodysplastic syndrome; COPD= chronic obstructive pulmonary disease; TIA = transient ischemic attack.

[a]Prior azacitidine use was not permitted.

Table 3

Adverse events (Grade 3–4) of interest by cycle: azacitidine vs CCR overall and by investigator preselection.[a].

	Number of patients[b] (%)					
	Azacitidine			CCR		
	Cycle 1–2 (*n* = 38)	Cycle 3–4 (*n* = 29)	Cycle 5–6 (*n* = 28)	Month 1–2 (*n* = 47)	Month 3–4 (*n* = 37)	Month 5–6 (*n* = 29)
Anemia	2 (5)	0	2 (7)	1 (2)	1 (3)	0
Neutropenia	15 (39)	8 (28)	7 (25)	6 (13)	3 (8)	2 (7)
Thrombocytopenia	14 (37)	8 (28)	5 (18)	10 (21)	2 (5)	3 (10)
Fatigue	0	1 (3)	1 (3)	0	1 (3)	0
Pyrexia	3 (8)	0	0	1 (2)	0	0
	Patients preselected for BSC, *n* (%)					
	Azacitidine			BSC		
	Cycle 1–2 (*n* = 27)	Cycle 3–4 (*n* = 21)	Cycle 5–6 (*n* = 20)	Month 1–2 (*n* = 32)	Month 3–4 (*n* = 27)	Month 5–6 (*n* = 22)
Anemia	2 (7)	0	1 (5)	0	1 (4)	0
Neutropenia	9 (33)	4 (19)	5 (25)	2 (6)	1 (4)	1 (5)
Thrombocytopenia	10 (37)	6 (29)	4 (20)	5 (16)	1 (4)	2 (9)
Fatigue	0	1 (5)	1 (5)	0	1 (4)	0
Pyrexia	2 (7)	0	0	0	0	0
	Patients preselected for LDAC, *n* (%)					
	Azacitidine			LDAC		
	Cycle 1–2 (*n* = 10)	Cycle 3–4 (*n* = 7)	Cycle 5–6 (*n* = 7)	Cycle 1–2 (*n* = 14)	Cycle 3–4 (*n* = 9)	Cycle 5–6 (*n*=7)
Anemia	0	0	1 (14)	1 (7)	0	0
Neutropenia	6 (60)	4 (57)	2 (29)	3 (21)	1 (11)	1 (14)
Thrombocytopenia	4 (40)	2 (29)	1 (14)	4 (29)	1 (11)	1 (14)
Fatigue	0	0	0	0	0	0
Pyrexia	1 (10)	0	0	1 (7)	0	0

Note: Table shows only the first 6 cycles. Patients continued to receive AZA or CCR until disease progression or intolerable toxicity.

[a] Only 1 patient received intensive chemotherapy; this patient is included in the CCR cohort, but is not presented in the preselection comparison.

[b] Safety population: 2 patients (1 randomized to BSC and 1 randomized to intensive chemotherapy) withdrew before receiving CCR.

Table 4

Adverse events (Grade 3–4) of interest over all cycles: azacitidine vs CCR and by investigator preselection.

	Safety population[a] (*n* = 85)		Investigator preselection[b]			
	Azacitidine (*N* = 38)	CCR (*N* = 47)	BSC (*n* = 59)		LDAC (*n* = 24)	
			Azacitidine (*N*= 27	BSC (*N* = 32)	Azacitidine (*N* = 10)	LDAC (*N* = 14)
Patients with ≥1 TEAE	31 (82)	34 (72)	22 (82)	26 (81)	9 (90)	7 (50)
Anemia	5 (13)	2 (4)	4 (15)	1 (3)	1 (10)	1 (7)
Thrombocytopenia	19 (50)	14 (30)	13 (48)	9 (28)	6 (60)	2 (29)
Neutropenia	23 (61)	8 (17)	15 (56)	4 (13)	8 (80)	3 (21)
Infection	15 (39)	12 (26)	12 (44)	7 (22)	3 (30)	4 (29)
Diarrhea	0	2 (4)	0	0	0	2 (14)
Pyrexia	3 (8)	1 (2)	2 (7)	0	1 (10)	1 (7)
Fatigue	1 (3)	1 (2)	1 (4)	1 (3)	0	0

TEAE = treatment emergent adverse event.

[a] Safety population: 2 patients (1 randomized to BSC and 1 randomized to intensive chemotherapy) withdrew before receiving CCR.

[b] Only 1 patient received intensive chemotherapy; this patient is included in the CCR cohort, but is not presented in the preselection comparison.

Table 5

Infections (any grade) of interest by cycle: azacitidine vs CCR.

	Number of patients[a] (%)					
	Azacitidine			CCR		
	Cycle 1–2 (*n* = 38)	Cycle 3–4 (*n* = 29)	Cycle 5–6 (*n* = 28)	Cycle[b] 1–2 (*n* = 47)	Cycle 3–4 (*n* = 37)	Cycle 5–6 (*n* = 29)
Bronchitis	2 (5)	2 (7)	1 (4)	2 (4)	1 (3)	1 (3)
Upper respiratory tract infection	0	0	2 (7)	1 (2)	0	1 (3)
Pneumonia	1 (3)	0	0	5 (11)	1 (3)	1 (3)
Sepsis	2 (5)	0	0	0	0	0
Urinary tract infection	2 (5)	1 (3)	0	1 (2)	0	0

Note: Table shows only the first 6 cycles. Patients continued to receive AZA or CCR until disease progression or intolerable toxicity.

[a]Safety population: 2 patients (1 randomized to BSC and 1 randomized to intensive chemotherapy) withdrew before receiving CCR.

[b]Calculated as months for BSC.