Impact of Azacytidine on the Quality of Life of Patients With Myelodysplastic Syndrome Treated in a Randomized Phase III Trial: A Cancer and Leukemia Group B Study

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Purpose: **The impact of azacytidine (Aza C) on the quality of life of 191 patients with myelodysplastic syndrome was assessed in a phase III Cancer and Leukemia Group B trial (9221).**

Patients and Methods: **One hundred ninety-one patients (mean age, 67.5 years; 69% male) were randomized to receive either Aza C (75 mg/m² subcutaneous for 7 days every 4 weeks) or supportive care, with supportive care patients crossing over to Aza C upon disease progression. Quality of life was assessed by centrally conducted telephone interviews at baseline and days 50, 106, and 182. Overall quality of life, psychological state, and social functioning were assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and the Mental Health Inventory (MHI).**

Results: **Patients on the Aza C arm experienced significantly greater improvement in fatigue (EORTC, *P* = .001), dyspnea (EORTC, *P* = .0014), physical functioning (EORTC, *P* = .0002), positive affect (MHI, *P* = .0077), and psychological distress (MHI, *P* = .015) over the course of the study period than those in the supportive care arm. Particularly striking were improvements in fatigue and psychological state (MHI) in patients treated with Aza C compared with those receiving supportive care for patients who remained on study through at least day 106, corresponding to four cycles of Aza C. Significant differences between the two groups in quality of life were maintained even after controlling for the number of RBC transfusions.**

Conclusion: **Improved quality of life for patients treated with Aza C coupled with significantly greater treatment response and delayed time to transformation to acute myeloid leukemia or death compared with patients on supportive care (*P* < .001) establishes Aza C as an important treatment option for myelodysplastic syndrome.**

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THE PROGNOSIS FOR patients with myelodysplastic syndrome (MDS) is grim, with an overall median survival for those with high-risk MDS ranging between 6 and 12 months.[1] Presently, no treatment has been proven effective, including antileukemia chemotherapy, hormonal therapy, and differentiation-inducing agents.[2,3] Allogeneic bone marrow transplantation (BMT) has offered the only real opportunity for cure, but because of treatment toxicity and the older age of the MDS population, it is an option for only a few individuals.[1,3]

In 1985, a new agent, azacytidine (Aza C) was tested for safety and efficacy in two phase II studies in patients with poor-risk MDS within the Cancer and Leukemia Group B (CALGB).[2] There was a demonstrated treatment response in 49% of 43 assessable patients (12% in complete remission; 25%, partial remission; and 12%, improved), with an overall median survival of 13.3 months. Transfusion requirements were eliminated in 82% (14 of 17) of patients who responded and had previously required RBC transfusions at study entry.[2] In the second study, Aza C was administered subcutaneously, with comparable results.[4]

On the basis of these findings, a phase III randomized trial was initiated in the CALGB (CALGB 9221) in 1993 to test the clinical efficacy of Aza C and its impact on quality of life.[5] It was hypothesized that a response to Aza C would result in improved quality of life attributable to better palliation, with less fatigue resulting in improved physical and social functioning and less psychological distress.

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PATIENTS AND METHODS

Research Procedures

All participants in the quality-of-life component of the clinical trial, CALGB 9221, had a diagnosis of MDS and on informed consent had been randomized to either Aza C (75 mg/m^2 for 7 days subcutaneously every 28 days) or supportive care.[5] Treatment arms were stratified by histologic subtype using French-American-British (FAB) criteria. Patients in both arms continued to receive best supportive care with transfusions, antibiotics, and hospitalizations. Eligibility requirements for the clinical trial were 16 years of age or older, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2,[6] and no other serious medical or psychiatric illness. After a minimum period of 4 months, those on the supportive care arm could cross over to the Aza C arm based on strict criteria concerning disease progression (see the study by Silverman et al in this issue of the *Journal of Clinical Oncology* for an extended description). Patients exited from the supportive care arm within the first 4 months only because of leukemic transformation or platelets less than 20×10^9/L.

Quality-of-life assessments were scheduled at the following times: study entry, before randomization; day 50 (corresponding to completing two cycles of Aza C, and 6 days before a bone marrow test to assess treatment response); day 106 (corresponding to completing four cycles of Aza C, and 7 days before re-evaluation of treatment response); and day 182, approximately 6 months after entry to the study, to capture any sustained quality-of-life benefits at the time of maximum treatment response, based on our previous experience.[2] Patients who crossed over from the supportive care arm to Aza C began the series of quality-of-life assessments again at that point. Quality-of-life assessment was discontinued when patients treated with Aza C either progressed or withdrew from the study.

Before randomization, patients were given a quality-of-life packet of measures on entry onto the clinical trial, with a request to complete it at home within 2 to 3 days. This was followed by a telephone interview generally lasting 30 to 40 minutes, conducted by two trained nurse research interviewers (E.P.D. and R.O.R). This procedure was repeated at all subsequent interviews, with the quality-of-life questionnaire packet mailed to patients 7 to 10 days before the scheduled interview. The use of centralized telephone interviews to collect quality-of-life data has been successfully used in numerous studies within the CALGB.[7]

Measures

The quality-of-life assessment consisted of standardized measures assessing patients' report of their physical symptoms and functioning, psychological state, and social functioning. All measures were administered at each assessment, except for sociodemographic questions, which were asked only at study entry, and the Perception of Improvement of Condition item, which was administered only to those taking Aza C at follow-up assessments.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 is a measure of quality of life applicable to patients with any cancer diagnosis, consisting of 30 items concerning general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning.[8,9] All subscale scores are transformed to a 0 to 100 scale. Higher scores on functional scales represented a better level of functioning; higher scores on symptom scales represented worsening symptoms.

Mental Health Inventory. The Mental Health Inventory (MHI),[10] a measure of psychological state, consists of 38 items grouped into the following five subscales: anxiety, depression, positive affect, emotional ties, and loss of behavioral and emotional control. The total score, the MHI index, and two global subscale scores, psychological distress and psychological well-being, are created from these subscales. Higher scores on the MHI index and subscales measuring positive affect and well-being indicate a better emotional state; higher scores on negative psychological states indicate a worse emotional state. The MHI has been tested on 5,000 respondents from six communities, which has served as the basis for the norms for the measure.[10]

Patients' perception of improvement in their condition. Patients randomized to the Aza C arm and those who later crossed over to treatment were asked at each follow-up assessment to rate whether they felt their condition was improving as a result of their treatment on an 11-point visual analog scale, from 0, "not at all," to 10, "complete improvement."

Sociodemographic and medical characteristics. Standard questions were used to obtain sociodemographic information at the time of interview,[11] and age and ethnicity were obtained at the time of patient registration. Medical information was collected from the medical record, including histologic diagnosis (as determined by central pathology review), ECOG performance status rating[6] at baseline, treatment response, and number of RBCs, platelet transfusions, and infections.

Statistical Considerations

Because of patient attrition over the course of the study attributable to disease progression, illness, and death, a pattern mixture model was used to analyze changes in quality of life over the study period, which took into account the number of quality-of-life assessments over time (ie, the pattern).[12,13] Patients were therefore categorized into four subgroups, based on the time of their last quality-of-life assessment, with subgroups generally coinciding with the number of assessments, as follows: subgroup 1, patients at study entry within 39 days after randomization, including a few patients with two assessments within this time interval; subgroup 2, mostly consisting of those assessed twice, with the last assessment occurring between days 40 and 82; subgroup 3, mostly consisting of patients assessed three times, with the last assessment conducted between days 83 and 159; and subgroup 4, mostly consisting of those assessed four times, with the last assessment conducted between days 160 and 259. These subgroups thus formed the patterns for the original two-arm design of the study. Within each subgroup, or pattern, a form of regression analysis, the linear random coefficient model, was used to test the effect of treatment arm and time on patients' quality of life. To statistically control for covariables to test the effect of crossing over to Aza C from supportive care on patients' quality of life, FAB subtypes and time elapsed after crossing over from the supportive care arm to Aza C were incorporated into the model. Data from subgroup 1 (n = 31) and subgroup 2 (n = 18) were combined in the analyses because of relatively small numbers in these subgroups and the assumption that treatment differences would be similar. For patients in the supportive care arm who crossed over to Aza C, subgroup classification was determined by the time from study entry to their last quality-of-life assessment on Aza C. It should be noted that although the original ideal points of assessment were study entry and days 50, 106, and 182, there was significant variability in the actual time patients were

assessed because of their illness or their being on vacation, delays in the mail, and interviewer and patient availability.

All of the quality-of-life measures were tested for significant differences between the treatment groups at baseline. The EORTC role functioning subscale was the only variable found to be significantly different at baseline between the two treatment arms. There were no other statistically significant differences between the two arms of the study for any of the remaining scales and subscales.

MHI scores were compared with norms for each of the subscales and total score to identify patients in severe distress with scores 1.5 SD above the norm.[10] Based on reports by Osoba et al[14] and King[15] that a 10-point change on the EORTC was comparable to a clinically significant improvement, the percentage of patients was calculated by treatment arm whose scores on EORTC subscales and total scores improved by 10 points or more at follow-up assessments from study entry levels.

Statistical Power Considerations

With 191 patients in the trial, the study had 80% power to detect a medium effect size of 0.57 (comparable with 0.54 of a SD, based on standardized means) between treatment arms in three quality-of-life measures for the change from baseline to the second follow-up assessment at day 106. Because there were three primary end points, MHI, EORTC fatigue subscale, and EORTC physical functioning subscale, the significance level used for determining the sample size was reduced to 0.017 (0.05/3) using Bonferroni's method.[16]

RESULTS

Patient Characteristics

One hundred ninety-one patients were accrued to the clinical trial from February 1994 to April 1996, with 99% having completed the baseline quality-of-life assessment. The mean age of patients was 67.5 years (SD, 10.3 years), and most were male (69%), white (93%), married (61%), and not presently employed (retired, 36%; disabled or unemployed, 23%) (Table 1). Our sample was more heavily represented by men than women than is usually indicated in epidemiologic studies.[1] There were no significant differences between the two treatment arms on study entry in any of the sociodemographic or medical characteristics.

Of the 99 patients initially randomized to Aza C, 56% (n = 56) remained on active treatment by day 182; 16% (n = 16) had died; 22% (n = 22) had terminated protocol treatment because of treatment failure, toxicity, or transformation to AML; and 5% (n = 5) refused to complete the quality-of-life questionnaires. Of the 92 patients initially randomized to supportive care, 47% (n = 43) remained on study with quality-of-life data collected through day 182, including 13% (n = 12) who remained on supportive care, 34% (n = 31) who remained on Aza C after cross-over, 23% (n = 21) who had died, 26% (n = 24) who had terminated protocol treatment, and 4% (n = 4) who refused to continue in the quality-of-life study. There were 80.4% (n = 74) and 61.9% (n = 57) of supportive care patients still on supportive care, completing quality-of-life assessments, at days 50 and 106, respectively.

Table 1. Patients' Medical and Sociodemographic Characteristics

Characteristic	Supportive Care (n = 92) (%)	Aza C (n = 99) (%)	Total (n = 191) (%)
Sex			
Male	65	73	69
Female	35	27	31
Race			
White	92	94	93
Black	5	3	4
Hispanic/Asian	2	3	3
Age			
30-49	5	7	6
50-59	13	10	12
60-69	40	37	39
70-79	27	36	32
80+	14	9	12
Mean ± SD, years	67.9 ± 10.3	67.3 ± 10.4	67.5 ± 10.3
Median, years	67	69	68
Range, years	35-88	31-92	31-92
Marital Status			
Married	65	58	61
Separated/divorced	5	6	6
Widowed	12	11	12
Single, never married	3	4	4
Unknown	14	21	18
Education			
1-11 grades	16	19	18
High school graduate	27	18	23
Some college/junior college degree	23	21	22
Bachelor's degree or higher	16	21	18
Unknown	18	20	19
Present employment			
Part- or full-time	24	17	20
Homemaker	3	3	3
Retired	36	35	36
Disabled/unemployed	21	24	23
Unknown	16	20	18
Performance status			
0	30	37	34
1	52	47	50
2	15	12	14
Unknown	2	3	3
Histology			
RA	20	19	19
RARS	3	4	4
RAEB	42	42	42
RAEB-T	20	22	21
CMMoL	7	6	6
Other	9	6	7

Abbreviations: RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation to leukemia; CMMoL, chronic myelomonocytic leukemia.

Comparison of Quality of Life of Patients on Aza C Arm Versus Supportive Care Arm

Over time, patients on the Aza C arm experienced significantly greater improvement in fatigue (EORTC, *P*

= .001), dyspnea (EORTC, $P = .0014$), physical functioning (EORTC, $P = .0002$), positive affect (MHI, $P = .0077$), and psychological distress (MHI, $P = .015$) than those in the supportive care arm (Tables 2, 3, and 4). As can be seen in Figs 1 through 4, which illustrate the EORTC fatigue, dyspnea, physical functioning, and MHI psychological well-being subscales, patients' quality of life for subgroups 3 and 4 was generally stable or worsening while on supportive care, compared with an improving quality of life for those on the Aza C arm. This was statistically demonstrated by the slopes of the regression lines for subgroups 3 and 4 often being in the opposite direction for the Aza C arm compared with the supportive care arm for many of the measures (Table 4 and Figs 1 through 4). Despite the considerable variability in patients' reporting of symptoms and functioning, as seen by the standard errors of the slopes in the regressions (Table 4), many of the differences between treatment arms were highly significant.

The correlations between the baseline measures of physical symptoms and functioning (ECOG performance status; EORTC subscales) with those of psychological state indicated a significant interrelationship between patients' physical status and psychosocial state (MHI psychological distress, $r = .17$ to $.46$; $P < .05$ to $< .0001$; median, $r = .30$; $P < .001$). These correlations suggested that physical improvement was the likely cause for the psychological improvement of patients taking Aza C.

Because RBC transfusions were more frequently administered in the Aza C group compared with the supportive care arm ($P = .002$) during the first month on study, it was possible that these transfusions were responsible for the significant improvements in patients' fatigue, physical functioning, and psychological state rather than Aza C. When RBC transfusions were statistically controlled for in the linear random coefficient model, significant differences between treatment arms were still maintained at the adjusted alpha level for the EORTC fatigue, dyspnea, physical functioning, and MHI psychological well-being subscales. The sole exception was the MHI psychological distress subscale, with treatment arm differences becoming nonsignificant at $P = .017$ (Bonferroni-adjusted alpha level),[14] on controlling for RBC transfusions ($P = .038$).

Quality-of-life measures before and after cross-over were compared for patients who had at least one quality-of-life assessment after cross-over (n = 38). Before cross-over, patients' quality of life was found to be either stable or slowly worsening, varying by quality-of-life area. However, subsequent to cross-over to Aza C, there was a significant improvement in the rates of change in several areas, comparable with those observed for the entire sample, including EORTC physical functioning, fatigue, dyspnea, and overall quality-of-life subscales and MHI global psychological distress and well-being subscales at the adjusted alpha level (Table 4). Figures 5 and 6, concerning several EORTC and MHI subscales, portray this for the 30 supportive care patients who crossed over to Aza C after approximately 4 months on supportive care and who were followed for a mean of 4 months on Aza C therapy. Patients also reported that their conditions were improving after cross-over to Aza C ($P = .0001$).

FAB histology subtypes were grouped into patients with better (refractory anemia [RA], RA with ringed sideroblasts; n = 44) and worse (RA with excess blasts, RA with excessive blasts in transformation to leukemia, chronic myelomonocytic leukemia; n = 133) prognoses[1] to test whether disease prognosis influenced the relationship between treatment arm and quality of life. There was no evidence of histologic subtypes significantly influencing patients' quality-of-life scores.

Clinical Significance

The ECOG performance status and MHI psychological distress subscale were used to examine whether the statistically significant differences in psychological status and physical functioning between treatment arms were clinically meaningful. The translation of the EORTC physical functioning scores to ECOG ratings at follow-up assessment from baseline levels was done by calculating the means of the EORTC physical functioning scale scores at baseline for the total sample for each of the ECOG ratings (ECOG 0 = 74.9; 1 = 62.7; 2 = 38.3). These scores then served as benchmarks for each of the ECOG ratings. The benchmark EORTC physical functioning means at baseline for ECOG 0, 1, and 2 were then subdivided into deciles matched to deciles we constructed between ECOG ratings of 0 and 1 and 1 and 2. The actual EORTC scores for each of the subgroups for each treatment arm were then compared with these benchmark EORTC decile means related to the decile ECOG ratings.

Using these values as benchmarks for a clinically meaningful change, the improvement in physical functioning in Aza C subgroup 3 patients at day 106 was comparable with an improvement in the ECOG score from approximately 1.3 to 0.7, whereas patients in the supportive care arm worsened from an ECOG status of 1.1 to 1.5 (see Table 5). Analyses of subgroup 4 were somewhat similar, with Aza C patients showing that an improved EORTC physical functioning score at day 182

Table 2. Means of Selected EORTC QLQ-C30 and MHI Scales for Each Subgroup for Supportive Care*

	Supportive Care											
	Baseline			F/U 1			F/U 2			F/U 3		
QoL Scale	Mean	No.	SD	Mean	No.	SD	Mean	No.	SD	Mean	No.	SD
EORTC												
Physical functioning†												
Subgroup 1	52.0	15	29.1	—	—	—	—	—	—	—	—	—
Subgroup 2	77.8	9	18.6	56.0	10	32.4	—	—	—	—	—	—
Subgroup 3	63.5	23	28.7	62.7	22	32.3	49.5	21	35.0	—	—	—
Subgroup 4	70.2	43	24.1	68.6	42	22.2	67.4	35	21.7	65.0	12	24.3
Fatigue‡												
Subgroup 1	47.8	15	22.5	—	—	—	—	—	—	—	—	—
Subgroup 2	42.8	9	18.6	47.4	10	22.8	—	—	—	—	—	—
Subgroup 3	34.1	22	26.7	42.5	21	24.5	47.2	21	27.4	—	—	—
Subgroup 4	39.5	43	24.3	37.9	41	18.3	38.0	35	17.8	42.2	12	24.3
Dyspnea‡												
Subgroup 1	35.3	15	29.3	—	—	—	—	—	—	—	—	—
Subgroup 2	36.7	9	11.0	43.0	10	27.4	—	—	—	—	—	—
Subgroup 3	27.3	23	21.6	25.5	22	20.2	33.1	21	23.5	—	—	—
Subgroup 4	26.1	43	19.8	30.6	42	19.8	34.9	35	19.5	30.3	12	26.2
Insomnia‡												
Subgroup 1	28.7	15	30.4	—	—	—	—	—	—	—	—	—
Subgroup 2	18.3	9	17.4	33.2	10	41.5	—	—	—	—	—	—
Subgroup 3	23.0	23	23.2	27.1	22	26.4	28.3	21	24.1	—	—	—
Subgroup 4	23.1	43	25.6	22.0	42	22.7	19.8	35	21.5	27.5	12	23.7
Social function†												
Subgroup 1	63.2	16	17.5	—	—	—	—	—	—	—	—	—
Subgroup 2	60.8	9	26.5	43.1	10	5.2	—	—	—	—	—	—
Subgroup 3	70.0	23	31.0	73.2	22	27.2	61.6	21	30.3	—	—	—
Subgroup 4	77.2	43	21.0	79.9	42	25.4	76.8	35	23.8	69.1	12	25.6
Overall QoL†												
Subgroup 1	46.3	16	14.9	—	—	—	—	—	—	—	—	—
Subgroup 2	53.6	9	25.8	38.3	10	22.7	—	—	—	—	—	—
Subgroup 3	50.8	23	28.3	54.6	22	28.0	39.3	21	26.6	—	—	—
Subgroup 4	56.9	43	20.2	58.9	41	18.9	56.6	35	20.5	51.3	12	21.5
MHI												
MHI index†												
Subgroup 1	166.5	16	24.4	—	—	—	—	—	—	—	—	—
Subgroup 2	170.7	9	34.7	160.6	10	36.3	—	—	—	—	—	—
Subgroup 3	187.3	23	20.1	185.0	22	25.2	181.0	21	29.6	—	—	—
Subgroup 4	170.2	43	26.0	175.6	42	22.7	177.6	35	22.1	169.4	12	22.8
Psychological distress‡												
Subgroup 1	52.6	16	13.9	—	—	—	—	—	—	—	—	—
Subgroup 2	50.2	9	19.9	55.2	10	22.4	—	—	—	—	—	—
Subgroup 3	39.9	23	9.5	43.1	22	13.3	44.6	21	17.8	—	—	—
Subgroup 4	50.9	43	15.1	46.4	42	12.3	45.3	35	11.5	48.3	12	11.0
Psychological well-being†												
Subgroup 1	53.1	16	11.9	—	—	—	—	—	—	—	—	—
Subgroup 2	54.9	9	16.5	49.8	10	16.3	—	—	—	—	—	—
Subgroup 3	61.2	23	12.6	62.1	22	13.5	59.6	21	14.0	—	—	—
Subgroup 4	54.9	43	12.6	56.0	42	12.5	56.7	35	12.3	51.8	12	12.7
Positive affect†												
Subgroup 1	35.4	16	9.1	—	—	—	—	—	—	—	—	—
Subgroup 2	37.2	9	12.5	33.3	10	13.3	—	—	—	—	—	—
Subgroup 3	41.3	23	10.7	42.4	22	11.2	40.0	21	11.4	—	—	—
Subgroup 4	36.9	43	10.3	37.9	42	9.8	38.0	35	10.0	34.3	12	10.1

NOTE. Subgroups generally coincided with the number of follow-up assessments, as follows: subgroup 1, one assessment or baseline assessment only; subgroup 2, two assessments or baseline + one follow-up at day 50; subgroup 3, three assessments or baseline through second follow-up at day 106; subgroup 4, four assessments or baseline through third follow-up at day 182.

Abbreviation: F/U, follow-up.

*Means for supportive care arm are before cross-over.

†Higher scores indicate better functioning.

‡Higher scores indicate worse symptoms.

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