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ORIGINAL REPORT

Multicenter Study of Decitabine Administered Daily for 5 Days Every 4 Weeks to Adults With Myelodysplastic Syndromes: The Alternative Dosing for Outpatient Treatment (ADOPT) Trial

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Decitabine, a DNA-targeted hypomethylating agent, is approved by the United States Food and Drug Administration for treatment of patients with myelodysplastic syndromes (MDS) on a schedule of 15 mg/m^2 administered via intravenous (IV) infusion every 8 hours for 3 days. This study assessed the efficacy and safety of an alternative dosing regimen administered on an outpatient basis in academic and community-based practices.

Patients and Methods
Patients were treated with decitabine 20 mg/m^2 by IV infusion daily for 5 consecutive days every 4 weeks. Eligible patients were ≥ 18 years of age and had MDS (de novo or secondary) of any French-American-British (FAB) subtype and an International Prognostic Scoring System (IPSS) score ≥ 0.5. The primary end point was the overall response rate (ORR) by International Working Group (IWG 2006) criteria; secondary end points included cytogenetic responses, hematologic improvement (HI), response duration, survival, and safety.

Results
Ninety-nine patients were enrolled; the ORR was 32% (17 complete responses [CR] plus 15 marrow CRs [mCRs]), and the overall improvement rate was 51%, which included 18% HI. Similar response rates were observed in all FAB subtypes and IPSS risk categories. Among patients who improved, 82% demonstrated responses by the end of cycle 2. Among 33 patients assessable for a cytogenetic response, 17 (52%) experienced cytogenetic CR (n = 11) or partial response (n = 6).

Conclusion
Decitabine given on a 5-day schedule provided meaningful clinical benefit for patients with MDS, with more than half demonstrating improvement. This suggests that decitabine can be administered in an outpatient setting with comparable efficacy and safety to the United States Food and Drug Administration–approved inpatient regimen.

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INTRODUCTION

The myelodysplastic syndromes (MDS) are a diverse group of clonal disorders characterized by bone marrow failure, dysplastic changes in hematopoietic cells, genomic instability, and progressive increase in marrow blast cells.[1] Abnormal cytosine methylation patterns are widespread in MDS, and hypermethylation-associated silencing of expression of tumor suppressor genes is thought to contribute to MDS pathobiology.[2,3]

Decitabine (5-aza-2′-deoxycytidine) is a cytidine analog approved for the treatment of all French-American-British (FAB) classification subtypes of MDS, including secondary MDS and previously treated patients. Although the precise mechanism of the clinical efficacy of decitabine is uncertain, two mechanisms of action have been proposed: direct cytotoxicity and hypomethylation, which may induce cell differentiation, reduce proliferation, and increase apoptosis.[4,5]

Two phase II clinical trials[6] of decitabine in patients with MDS resulted in overall improvement rates (complete response [CR], partial response [PR], and hematologic improvement [HI]) of 42% and 55%. In the phase III study that led to United States Food and Drug Administration approval of decitabine for MDS, decitabine was administered every 6 weeks at a dose of 15 mg/m^2 given intravenously (IV) over 3 hours every 8 hours for 3

consecutive days (135 mg/m^2 per course), and the overall improvement rate (International Working Group [IWG] 2000 response criteria)[7] for patients who received decitabine was 30%, versus 7% for patients receiving supportive care alone.[8]

Subsequently, Kantarjian et al[9] explored several decitabine dosing schedules that could be administered in the outpatient setting. In their single-center study, patients with MDS received one of three schedules of decitabine: 20 mg/m^2 IV over 1 hour daily for 5 days, 10 mg/m^2 IV over 1 hour for 10 days, or 10 mg/m^2 subcutaneously twice a day for 5 days. The best response rate was seen in the 5-day IV arm (39% CR plus 22% marrow CR [mCR] by IWG 2006 criteria for the first 95 patients enrolled). The purpose of the present study was to further assess the efficacy and safety of this 5-day outpatient decitabine regimen in a multicenter setting, including both academic institutions and community-based practices.

PATIENTS AND METHODS

Patients

The study was approved by the institutional review boards of participating centers. All patients provided written informed consent. Eligible patients were older than 18 years of age and were required to have a diagnosis of MDS (de novo or secondary) of any FAB subtype, including chronic myelomonocytic leukemia (CMML) with a WBC less than 12×10^9/L. Patients with refractory anemia and refractory anemia with ringed sideroblasts FAB types were required to be RBC transfusion-dependent (ie, requiring transfusion at least every 4 weeks). Patients were required to have undergone bone marrow aspiration/biopsy with cytogenetic evaluation within 28 days of enrollment and have an International Prognostic Scoring System (IPSS) score of ≥ 0.5. An IPSS score was assigned to all patients, including those with secondary MDS or prior therapy, although the IPSS was based on untreated patients with de novo MDS and has not been formally validated in other subgroups. Additionally, patients were required to have adequate renal and hepatic function and an Eastern Cooperative Oncology Group performance status of 0 to 2.

Patients who received epoetin or darbepoetin before study enrollment were required to have been on a stable dose for at least 8 or 12 weeks, respectively, before the first decitabine dose. Patients with a previous diagnosis of acute myeloid leukemia or a concurrent malignancy were excluded, as were patients who had received androgenic hormones or granulocyte colony-stimulating factors within 7 days of study initiation (21 days for pegfilgrastim), investigational agents within 30 days of study initiation, or azacitidine or decitabine at any time.

Study Design

The study was multicenter, nonrandomized, and open-label. Decitabine was administered as a 20 mg/m^2 IV dose once daily over 1 hour for 5 consecutive days every 4 weeks. Treatment response was assessed by weekly CBCs and bone marrow examination every two cycles until a CR was confirmed. Bone marrow samples for all patients were reviewed by local pathologists and by a central reviewer. In addition, an independent external reviewer assessed patient classifications and responses.

No dose reductions or escalations of decitabine were allowed, although treatment could be delayed at the discretion of the treating physician if patients experienced disease-related or treatment-related complications. Treatment was resumed when these complications improved or resolved. Patients continued to receive study drug until one of the following occurred: death, disease progression, intercurrent illness preventing further administration of treatment, unacceptable adverse event, decision by the patient to withdraw from the study, or if, after four cycles, the treating physician believed the patient had not received any clinical benefit.

Patients were permitted to receive supportive care, including transfusions, antibiotics, and treatment for complications such as febrile neutropenia. Filgrastim and pegfilgrastim or sargramostim were only permitted if patients experienced severe infections or sepsis. Interleukin-11 and thrombopoietic agents were not permitted.

Study End Points and Response Assessment

Data presented reflect a May 31, 2007 data cutoff date, which was 1 year after the last patient enrolled onto the study. The primary end point of overall response rate (ORR) was assessed by a central reviewer according to both the 2000 IWG criteria and the revised 2006 criteria; the 2006 criteria were used to report results here.[10] According to the 2006 IWG criteria, a CR is defined as normalization of peripheral counts (hemoglobin $>$ 11 g/dL without transfusion or erythropoietin use, neutrophils $\geq 1.0 \times 10^9$/L in the absence of growth factor use, and platelets $\geq 100 \times 10^9$/L without transfusion or growth factors) and bone marrow blasts less than 5% for at least 4 weeks; mCR is defined by $\geq$ 50% myeloblast reduction from more than 5% myeloblasts to $\leq$ 5%, but without recovery of peripheral counts to a level meeting criteria for CR. Criteria for a PR are the same as for CR, except for a decrease of $\geq$ 50% in the percentage of blasts over pretreatment (but still $>$ 5%), or improvement to a less advanced MDS FAB classification than pretreatment.

Secondary end points in the study included cytogenetic responses, HI, overall survival, transfusion requirements, and safety.[10] HI-erythroid (HI-E) lineage responses were not recorded for the 15% of patients who were receiving stable doses of darbepoetin or epoetin as concomitant therapy. Duration of response was defined as the interval from the date that a CR or PR was documented to the date that the patient experienced recurrence/progression of disease. For patients still experiencing a response at the time of the data cutoff, censoring occurred at the last CBC and/or bone marrow assessment.

Overall survival was calculated from the date of the first dose of study drug to the date of death from any cause. Transfusion requirements were recorded for each patient for the 8-week period before the first study drug dose and throughout the trial. Transfusion independence was defined by lack of requirement for transfusions for at least 8 weeks. Adverse events were assessed by the investigators using Common Toxicity Criteria for Adverse Events version 3.0. Adverse drug reactions were defined as those with a causality of at least possibly related to decitabine use.

Statistical Analysis

Days to initial response, duration of response, overall improvement, and overall survival were calculated using Kaplan-Meier product limit estimates, along with 95% CIs.

RESULTS

Patient Demographics

This study enrolled a total of 99 patients at 28 North American sites; no single site enrolled more than 15% of patients. The median age was 72 years (range, 34 to 87 years), and the median time from diagnosis of MDS was 22 weeks (range, 1 to 440 weeks; mean, 63 weeks). Most patients (89%) had apparent de novo MDS, and 27% of patients had received prior "active" MDS therapy (ie, not just growth factors), which included treatment with cytotoxics, immunomodulatory agents, and stem-cell transplantation. The distribution of IPSS risk groups as assigned by investigators included high (23%), intermediate-2 (23%), intermediate-1 (53%), and low (1%) risk categories. Independent expert review of IPSS risk groups differed modestly from investigator assessments, primarily as a result of modest differences in assessment of marrow blast proportion: high (24%), intermediate-2 (32%), intermediate-1 (28%), and low (4%).

At baseline, 67% of patients were RBC transfusion-dependent, and 15% were platelet transfusion-dependent. One half of assessable patients had abnormal cytogenetic findings before treatment.

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients	%
No. of patients (ITT)	99	
Age, years		
Mean	71	
Median	72	
Range	34-87	
Male sex	71	72
Race/ethnicity		
White	86	87
Black or African American	6	6
Asian/other/mixed	7	7
ECOG performance status		
0	37	37
1	51	52
2	11	11
Time from diagnosis to first dose day, weeks		
Mean	63	
Median	22	
Range	1-440	
Type of MDS		
De novo	88	89
Secondary	11	11
Patients with prior active MDS therapy*	27	27
Cytotoxics	14	14
Immunosuppressive agents	14	14
Stem-cell transplantation	1	1
FAB classification†		
RA plus RARS‡	37	37
RAEB plus RAEB-T	51	52
CMML	11	11
IPSS risk group§‖		
Low	1	1
Intermediate 1	52	53
Intermediate 2	23	23
High	23	23
Cytogenetic classification of risk		
Good	49	49
Intermediate	15	15
Poor	29	29
Unknown	6	6
Cytogenetic abnormalities		
Normal	44	44
Deletion 5q	12	12
Deletion 20q	3	3
Chromosome 7	18	18
Complex	19	19
+8	10	10
−Y	5	5
Other	13	13
Not evaluated	6	6
Myeloblasts		
< 5%	42	42
5% to < 10%	13	13
10% to < 20%	33	33
≥ 20%	10	10
Unknown	1	1

Abbreviations: ITT, intent to treat; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; CMML, chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System.

*Patients could have received more than one type of prior active MDS therapy, which included cytotoxics (hydroxycarbamide [hydroxyurea] [6%], cytarabine [5%], arsenic trioxide [3%], bortezomib, cyclophosphamide, daunorubicin, idarubicin, oblimersen sodium [all 1%]), immunomodulatory agents (antithymocyte immunoglobulin [1%], cyclosporine [4%], lenalidomide [3%], thalidomide [9%]) and stem-cell transplantation [1%]. In addition to these therapies, 65% of patients had previously received an erythropoiesis-stimulating agent (epoetin or darbepoetin).

†Expert review of FAB classification: RA plus RARS (23%), RAEB plus RAEB-T (57%), CMML (8%).

‡Patients had to be RBC transfusion-dependent.

§Expert review of IPSS classification: low (4%), intermediate-1 (28%), intermediate-2 (32%), high (24%).

‖IPSS was assigned to all patients, including those with secondary MDS or prior therapy.

Investigator-assessed IPSS risk stratification of cytogenetic findings was good in 49%, intermediate in 15%, and poor risk in 29%; karyotyping was unsuccessful or results were not available in 6%. Patient characteristics are detailed in Table 1.

Response

In this trial, 32 of the 99 patients experienced CR (n = 17) or mCR (n = 15; ORR, 32%; 95% CI, 23% to 43%), and another 18 patients experienced HI (overall improvement rate, 51%; 95% CI, 40% to 61%; Table 2). Seventy-five percent of patients experienced stable disease (SD) or better. When responses were evaluated using the 2000 IWG criteria, the overall improvement rate was 43% (95% CI, 34% to 54%), including 15 patients with a CR.

Of the 50 patients who experienced clinical improvement, initial responses were detected by the end of two cycles in 82% of cases (Fig 1). Fifty-four percent of the 50 patients who experienced clinical improvement had their best response within the first two cycles. The median time to initial improvement was 1.7 months (95% CI, 36 to 53 days) and the median duration of improvement was 10 months (95% CI, 204 days to not estimable). Response duration has been up to 17 months in a patient who was still receiving treatment at the data cutoff point.

Analysis of response by MDS patient subtypes is shown in Table 3. Activity was demonstrated across investigator-assessed IPSS risk groups, with an overall improvement rate of 50% for intermediate-1 patients, 61% for intermediate-2 patients, and 43% for high-risk patients. A similar range of activity was noted within each IPSS risk group when assessed by the expert-classified IPSS (Table 3). Patients who were classified as having CMML (n = 11) had a 73% improvement rate.

Table 2. Responses to Decitabine Treatment

	ITT (N = 99)	
Response by 2006 IWG Criteria	No. of Patients	%
Overall complete response rate, CR + mCR	32	32
Overall response rate, CR + mCR + PR	32	32
Overall improvement rate, CR + mCR + PR + HI	50	51
Rate of stable disease or better, CR + mCR + PR + HI + SD	74	75
CR	17	17
mCR	15	15
PR	0	0
HI	18	18
SD	24	24
PD	10	10
Not assessable*	15	15

Abbreviations: IWG, International Working Group; ITT, intent to treat; CR, complete response; mCR, marrow CR; PR, partial response; HI, hematologic improvement; SD, stable disease; PD, progressive disease.

*A total of 15 patients were not assessable for a response assessment because post-therapy bone marrow and/or CBC values were not available. Specifically, five patients were entered onto the study with comorbid conditions (including metastatic lung cancer, preexisting acute respiratory distress syndrome, pulmonary fibrosis, and cardiomyopathy) that resulted in early withdrawal from the study and precluded an opportunity for a response assessment, five patients were withdrawn from the study early for administrative reasons (ie, patient or family decision) without documentation of a study-related adverse event, and five patients had adverse events before the first post-therapy bone marrow evaluation and were withdrawn based on the clinical judgment of the investigator.

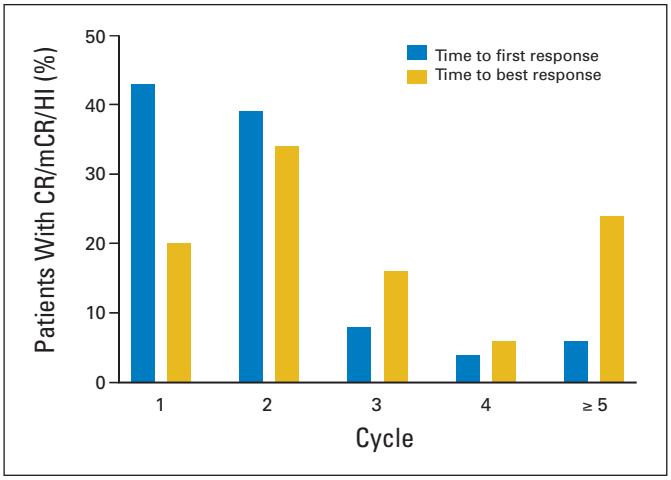

Fig 1. Time to first response and best response by cycle (n = 50). CR, complete response; mCR, marrow CR; PR, partial response; HI, hematologic improvement.

Improvement was observed in patients regardless of time from MDS diagnosis (≤ 1 year, 56% [22% CR] and ≥ 1 year, 42% [8% CR]), but fewer CRs occurred in patients with disease duration longer than 1 year. In the 72 patients who had not received prior active MDS therapy, the overall improvement rate was 53%, with 14 CRs (19%), 11 mCRs (15%), and 13 HIs (18%); in patients with prior therapy, the overall improvement rate was 44%, with three CRs (11%), four mCRs (15%), and five HIs (19%).

Thirty-three patients were assessable for cytogenetic response (ie, had abnormal cytogenetic findings at baseline, and cytogenetic data for at least one post-treatment marrow analysis). The overall cytogenetic response rate in this subset was 52%, with 11 cytogenetic CRs and six PRs (> 50% reduction in abnormal metaphases). The median time to cytogenetic response was 2.3 months, coinciding with the first post-treatment marrow sampling timing. Of the 17 cytogenetic responders, 76% had a clinical response (CR or mCR), and 53% had IPSS poor-risk cytogenetics at baseline.

Survival

The 1-year survival rate for patients treated with decitabine was 66%. Median survival was 19.4 months (95% CI, 15 months to not estimable). At the data cutoff date, 42 patients had died and 57 patients were being observed for survival, including 13 patients who were still being treated. Survival analyses by FAB subtype and IPSS score are shown in Figure 2.

Treatment With Decitabine

Patients received a median of five cycles of decitabine therapy (range, one to 17 cycles), and 38% of patients received eight or more cycles. A total of 619 cycles were initiated, and all five doses of a cycle were administered in 98% of cycles. Consistent with the dosing regimen of this trial, the median cycle duration was 28 days.

During the course of the trial, 87% of patients discontinued treatment for a variety of reasons, including progression of disease (19%); investigator decision, most commonly because of inadequate response (18%); adverse event (15%); personal decision (13%); death (12%); nonadherence (1%); and other considerations (8%).

Table 3. Overall Improvement (2006 IWG criteria) to Decitabine by Subgroup

Subgroup	Patients With Overall Improvement (CR + mCR + PR + HI)	Total No. of Patients in Subgroup	%
Time from diagnosis to first dose, years			
< 1	35§	63	56
> 1	15	36	42
Type of MDS			
De novo	45§	88	51
Secondary	5	11	45
Patients with prior disease-modifying MDS therapy*			
No	38§	72	53
Yes	12	27	44
FAB classification†			
RA + RARS‡	15§	37	40
RAEB + RAEB-T	27	51	53
CMML	8	11	73
IPSS risk group‖¶			
Intermediate-1	26§	52	50
Intermediate-2	14	23	61
High	10	23	43
Cytogenetic classification of risk			
Good	26§	49	53
Intermediate	10	15	67
Poor	12	29	41

Abbreviations: IWG, International Working Group; CR, complete response; mCR, marrow CR; PR, partial response; HI, hematologic improvement; MDS, myelodysplastic syndrome; FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; CMML, chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System.

*Patients could have received more than one type of prior disease-modifying therapy.

†Improvement rates by expert reviewer's FAB classification: RA+RARS (30%), RAEB+RAEB-T (56%), CMML (75%).

‡Patients with RA or RARS were required to have been red cell transfusion dependent to enroll.

§Observed differences in overall improvement rates between subgroups did not achieve statistical significance.

‖IPSS was assigned to all patients, including those with secondary MDS or prior therapy.

¶Improvement rates by expert reviewer's IPSS classification: Intermediate-1 (46%), Intermediate-2 (59%), High (50%).

Transfusion Status

Of the 66 patients who were RBC transfusion-dependent at baseline, 22 patients (33%) became RBC transfusion-independent during the study. Although an increased need for RBC transfusions was observed in the first cycles, transfusion-independence seemed to increase in later cycles as treatment continued (Appendix Fig A1, online only). Of the 15 patients who were platelet transfusion-dependent at baseline, six patients (40%) became transfusion-independent during the course of the study.

Adverse Events

As expected, cytopenias were the most frequent complication (Table 4). Grade 3 or higher neutropenia, thrombocytopenia, febrile neutropenia, and anemia considered to be at least possibly related to the study drug occurred at rates of 31%, 18%, 14%, and 12% of patients, respectively. The majority of febrile neutropenia

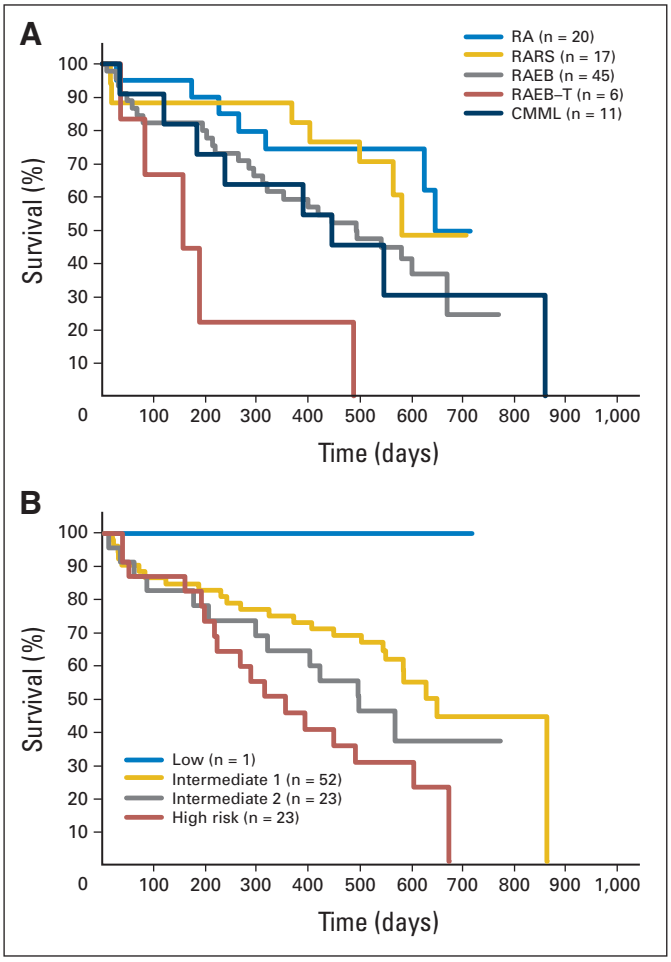

Fig 2. Kaplan-Meier survival analysis of enrolled patients stratified according to (A) French-American-British subtype of myelodysplastic syndrome and (B) International Prognostic Scoring System score. RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; CMML, chronic myelomonocytic leukemia.

Table 4. Summary of Adverse Events Occurring in ≥ 10% of Patients

Event	% of Patients	
	Grade 1-2	Grade ≥ 3
Hematologic		
Neutropenia	1	31
Thrombocytopenia	2	18
Febrile neutropenia	3*	14
Anemia	5	12
Nonhematologic		
Fatigue	26	5
Nausea	26	1
Pyrexia	17	0
Diarrhea	12	0
Anorexia	12	0
Constipation	11	0
Pneumonia	1	11
Vomiting	10	1
Chills	10	0

*Investigator assessed grade 1 febrile neutropenia; one patient did not meet the Common Toxicity Criteria for Adverse Events version 3.0 temperature criteria; the other two patients' febrile neutropenia could not be verified.

occurred within the first cycle (10% of enrolled patients); this complication was less common in subsequent cycles. Grade 3 or worse nonhematologic adverse events included pneumonia (11%) and fatigue (5%). Of the 619 cycles administered, 198 (32%) were delayed, primarily due to myelosuppression, with a median delay of 8 days, and there were 119 hospitalizations (19% of cycles were associated with a hospitalization). This is virtually identical to the previously reported single-institution study, in which 18% of 622 cycles of therapy were associated with hospitalization. Overall, 65% of patients were hospitalized at some point during the study (most in cycles 1 or 2), whereas in the single-institution study, 66% of patients were hospitalized.

Most patients who developed infectious complications had additional risk factors for infection, including preexisting severe neutropenia (absolute neutrophil count $< 0.5 \times 10^9$/L) or a history of disease-related infections. Eleven patients (11%) died within 30 days of receiving decitabine. In five of these patients, the local investigator determined that the death was unrelated to study therapy (progression of disease in three patients; pneumonia, myocardial infarct in one patient; and congestive heart failure in one patient). The remaining six patients had fatal adverse events that investigators considered possibly related to drug therapy, including pneumonia (n = 2), sepsis (n = 2), hepatic failure (n = 1), and subdural hemorrhage (n = 1). Of these 11 patients, seven had received only one cycle of therapy, two had received three cycles, one had received four cycles, and one had received seven cycles.

DISCUSSION

The outpatient decitabine regimen studied in this trial produced a 51% overall improvement rate (IWG 2006), with responses across all subtypes of MDS. Notably, 52% of patients had more than 1 year disease duration, 37% had prior therapy, and 12% had secondary MDS. There was a trend toward a better response rate in patients without these characteristics, as in a previous report correlating higher likelihood of decitabine response with shorter disease duration.[15] This suggests that patients with MDS have the potential to benefit from decitabine therapy, regardless of MDS subtype or risk factors, but response may be more likely if treatment takes place earlier in the disease course.

Differences in patient populations, exposure to prior therapy, disease duration, and other factors complicate a direct comparison of these trial results with other hypomethylating agent treatment studies. Despite these challenges, comparison of these trial results with prior decitabine studies indicates that the 43% overall improvement rate by IWG 2000 observed in this trial compares favorably with the phase III trial results that led to United States Food and Drug Administration approval of decitabine (30% overall improvement rate per IWG 2000).[8] This multicenter trial also confirms the clinical efficacy of the 5-day decitabine regimen reported in the single-institution study of Kantarjian et al.[9] However, the ORR (17% CR plus 15% mCR plus 0% PR = 32%) in our trial differs considerably from the ORR (39% CR plus 22% mCR plus

1% PR = 62%) reported with the same decitabine dose and schedule in the single-center trial, even though the single-center trial may have enrolled somewhat higher-risk patients (32% secondary MDS *v* 11% here, and 66% IPSS intermediate-2 or high-risk MDS *v* 46% here). In addition to the inherent differences between single- and multicenter trials, patient selection or patient management differences may have contributed to these varying results: the median number of treatment cycles administered was five here and nine in the single-center study; the single-center study had a higher proportion of assessable patients who received at least two cycles of therapy; and the trial reported here used dose delays to manage treatment-related cytopenias, instead of the dose reductions employed in the single-center trial. In addition, antimicrobial prophylaxis was universally used in the single-center trial, but in this study, individual investigators' usage of antimicrobial agents varied.

The 52% cytogenetic response rate observed here is similar to the 51% cytogenetic response rate in the single-center trial and suggests decitabine may alter the natural course of MDS. Of interest, patients who were classified as having CMML had an especially encouraging improvement rate (73%), comparable to the response rates reported previously.[8,11,12]

The ORR (CR plus mCR) of 32% in this multicenter trial includes the mCR category, one of the major additions to the 2006 IWG criteria compared with the 2000 IWG criteria. The clinical importance of mCR is uncertain, but may be of value in the allogeneic transplantation setting, where decitabine may induce rapid myeloblast reduction before initiation of transplant conditioning regimens, with less risk than with more intensive approaches.

Patients responding to decitabine in this study tended to do so promptly; 82% showed first improvement by the end of cycle 2. Although an early indication of improvement is clinically useful, it is not yet possible to predict a priori who will ultimately respond. Additionally, 24% of patients required more than five cycles to achieve best response, highlighting the need to administer an adequate trial of therapy before discontinuing. Once response is achieved, continued treatment may be necessary to maintain response.[13]

Fourteen percent of patients experienced febrile neutropenia in this study, and at least two deaths were attributed to infection. Although prophylactic antimicrobial agents were not mandated by this protocol, they should be considered for patients receiving decitabine treatment, especially for patients who are neutropenic at the onset of therapy.[14]

In summary, this alternative dose and schedule of decitabine provided clinical benefit to a substantial proportion of patients with MDS and can be administered in the outpatient setting. The efficacy and safety of this regimen is comparable to the regimen approved by the United States Food and Drug Administration, and treatment in the outpatient setting may offer increased convenience to patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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