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The Effect of Decitabine Dose Modification and Myelosuppression on Response and Survival in Patients With Myelodysplastic Syndromes

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Abstract

Myelosuppression in myelodysplastic syndromes (MDS) is associated with the hypomethylating agent decitabine. A retrospective pooled analysis of 2 decitabine clinical trials in patients with MDS conducted Cox regression analyses of red blood cell or platelet dependence, myelosuppression, dose modification, cycle delay or dose reduction, and survival effects. In 182 patients, baseline platelet dependence was a predictor for dose modification, reduction, or delay, and death (modification: $P = .006$, hazard ratio [HR] = 2.04; reduction/delay: $P = .011$, HR = 2.00; death: $P = .003$, HR = 1.94). Patients with dose modifications had significantly higher overall response rates versus those with none (22% vs 10%; $P = .015$). Patients with no dose modifications had faster progression to AML versus patients with dose modifications ($P = .004$). Without dose modifications, patients tended to drop out due to disease progression or other reasons. Decitabine dose modifications on treatment may indicate response to treatment.

Keywords

Dacogen; decitabine; myelodysplastic syndromes; retrospective study

INTRODUCTION

Myelodysplastic syndromes (MDS) are typically characterized by cytopenias and dysplasias of at least 2 of the 3 hematopoietic cell types. These heterogeneous disorders may involve

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Contributions: Study conception and design: GG-M, EJ, FR contributed to the study's conception and design. JC, ND, GG-M, EJ, TK, HK provided study materials or patients. MC, GG-M, EJ collected and assembled the data. JC, GG-M, EJ, HK, AT provided data analysis and interpretation. GG-M, EJ, HK prepared the manuscript. All authors critically reviewed and revised the manuscript, and provided final approval of the paper.

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megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in precursors of myeloid and erythroid cells, and malformed megakaryocytes [1,2]. More common in older individuals, MDS has a median age of onset of 65 to 70 years [1]. Irregular DNA hypermethylation is a hallmark of MDS and results in the silencing of tumor suppressor genes, providing these hematopoietic cells with a growth advantage [3,4]. Thus, in recent years, epigenetic therapy with hypomethylating agents has been introduced as a new strategy for the treatment of patients with MDS [5].

Decitabine (5-aza-2'-deoxycytidine) is a hypomethylating agent approved by the US Food and Drug Administration for the treatment of patients with MDS. Its mechanism of action is thought to involve direct cytotoxicity and/or induction of DNA hypomethylation [5,6]. Two approved dosage regimens are recommended for a minimum of 4 treatment cycles: (1) a 3-day regimen of decitabine 15 mg/m² infused intravenously over 3 hours every 8 hours for 3 consecutive days, every 6 weeks, and (2) a 5-day regimen of decitabine 20 mg/m² infused intravenously over 1 hour once daily for 5 consecutive days, every 4 weeks [6]. A recent analysis of methylation changes during decitabine treatment in a subset of patients with MDS in a phase III trial of decitabine (3-day regimen; NCT00043381, described below) found that reduced methylation over time was correlated with treatment response. Investigators reported a 41% decrease in methylation in patients with a complete or partial response, a 10% decrease in methylation in patients with hematologic improvement, a 15% increase in methylation in patients with stable disease, and a 27% increase in methylation in patients with progressive disease [7].

A low white blood cell count is a feature of MDS, and myelosuppression is an adverse effect of decitabine treatment [6]. For example, the incidence of thrombocytopenia alone in a population of 2410 patients at referral at the MD Anderson Cancer Center who were diagnosed with primary or secondary MDS with or without prior treatment was 67% [8]. Consequently, decitabine dose modifications are recommended in response to on-treatment myelosuppression [6].

The effects of myelosuppression and decitabine dose modification on disease response and patient survival have not been determined. It is possible that administration of decitabine could affect both abnormal and normal rapidly dividing marrow cells during a susceptible phase of the cell cycle, with myelosuppression heralding decitabine activity. In contrast, prolonged myelosuppression, regardless of cause, may portend less desirable outcomes. The objective of this analysis was to determine the effects of decitabine dose modification and myelosuppression on treatment response and survival in patients with MDS receiving decitabine therapy.

MATERIALS AND METHODS

Study Design and Patients

This was a retrospective analysis of a pooled subset of data from patients with MDS enrolled in 2 clinical trials of decitabine: a phase III trial of the 3-day dosage regimen (Study D-0007, conducted between July 2001 and January 2004 at 23 sites) [9] and a phase II trial of the 5-day dosage regimen (Study DACO-020, conducted between June 2005 and March 2008 at

28 sites) [10]. Both multicenter studies enrolled patients at least 18 years of age in the US and Canada and had similar inclusion and exclusion criteria. Patients had de novo or secondary MDS, either of intermediate or high risk [9] or of any French-American-British (FAB) subtype [10]. Each study allowed the administration of blood products and prophylactic antibiotics as supportive care and the administration of granulocyte colony-stimulating factor for the treatment of serious infection or sepsis [9,10]. The institutional review board of each investigational site approved the relevant study protocol, and all participants provided written informed consent prior to enrollment. Both trials were registered with ClinicalTrials.gov (Study D-0007 identifier: NCT00043381; Study DACO-020 identifier: NCT00260065).

In the D-0007 study (3-day regimen), decitabine dose modifications included cycle delays and dose reductions that were instituted if hematologic recovery (absolute neutrophil count $1,000/\mu\text{L}$ and platelets $50,000/\mu\text{L}$) from a previous treatment cycle required more than 6 weeks but less than 8 weeks (cycle delayed by up to 2 weeks and dose temporarily reduced) or more than 8 weeks but less than 10 weeks (cycle delayed by up to another 2 weeks and dose reduced). Any patient requiring 10 weeks or longer to recover was withdrawn from the study. If any of the following nonhematologic toxicities occurred, the decitabine dose was delayed until the toxicity resolved: serum creatinine 2 mg/dL ; alanine aminotransferase or total bilirubin 2 times the upper limit of normal; or the presence of active or uncontrolled infection. Cycle delay was defined as the duration of the first day of cycle-to-cycle being more than 8 weeks, and dose reduction was defined as the administration of 11 mg/m^2 every 8 hours, as stated in the prescribing information for decitabine [6].

In the DACO-020 study (5-day regimen), no dose reductions or escalations were allowed. Cycle delays were permitted at the discretion of the investigator for myelosuppression (defined as anemia, neutropenia, leukopenia, or thrombocytopenia), infection, hemorrhage, and renal or hepatic dysfunction.

This pooled analysis included patients from each trial who received at least 1 dose of decitabine. Dose modification was defined as all delay, reduction, interruption, and other (dose adjustment = “other”).

Study Evaluations

End points evaluated were best overall response rate (ORR; complete response [CR] rate + partial response [PR] rate), which was based on the 2000 International Working Group (IWG) response criteria for MDS [11], overall survival (OS), predictors of dose modification, predictors of response, and predictors of progression to acute myeloid leukemia (AML). In each study, best response to treatment and disease progression was assessed by the investigator based on evaluations of bone marrow aspirates, biopsies, and blood counts by a local pathologist. In Study D-0007, bone marrow aspirates and biopsies were taken every 12 weeks and the patient’s best hematologic response was noted as CR, PR, hematologic improvement (HI), stable disease (SD), or disease progression (PD), or transformation to AML according to the MDS IWG criteria. In Study DACO-020, evaluations were to be done within 7 days before chemotherapy cycle 3 and every other

cycle thereafter (ie, every 8 weeks) until confirmation of a CR by the investigator. Each patient was counted only once at their best response.

Statistical Analysis

A categorical analysis was undertaken to compare differences in the ORR and the incidence of grade 3 or 4 myelosuppression between patients with and without dose modification and between patients with and without cycle delays or dose reductions with the chi-square test. The Wald chi-square test was used to compare Kaplan-Meier curves for estimates of OS and progression to AML between patients with and without dose modifications and patients with and without cycle delays or dose reductions, adjusted for a time-dependent variable. Cox regression analyses were conducted for time to on-study red blood cell (RBC) or platelet dependence, occurrence of myelosuppression, dose modification, cycle delay or dose reduction, progression to AML, and survival as affected by baseline variables and time-dependent covariates. The variables analyzed were study, sex, age, race, International Prognostic Scoring System (IPSS) classification, growth factor support (transfusions), FAB classification, baseline platelet count, baseline RBC count, and myelosuppression.

Role of the Funding Source

Eisai Inc. financially supported data analysis and provided financial support for editorial assistance with manuscript preparation, including medical writing, editing, and graphics assistance. Angela Teng of Eisai Inc. analyzed the pooled data. All authors had access to the clinical trial data from the original studies, as well as all data from the pooled analyses.

RESULTS

Patients

This retrospective analysis included 182 patients who received at least 1 dose of decitabine; 83 of 89 patients randomized to decitabine in Study D-0007 and all 99 patients randomized to decitabine in Study DACO-020 were eligible. The demographic and baseline characteristics of patients who received decitabine in either study and who were included in the pooled analysis population are summarized in Table I. In the pooled analysis population, approximately 70% were men, most patients (87%) had de novo MDS, and approximately one third of patients had poor cytogenetic status. At baseline, most patients in the pooled analysis population had grade 1 or higher thrombocytopenia ($<100 \times 10^9/L$; 67%), neutropenia ($<1.5 \times 10^9/L$; 59%), and anemia ($<10 \text{ g/dL}$; 69%); the majority of patients (71%) were RBC transfusion dependent; and most (81%) were platelet transfusion independent.

Dose Modifications and Myelosuppression

The proportions of patients who had grade 3 or 4 myelosuppression and required dose modification (including cycle delays or dose reductions) are summarized in Table II. For the pooled data, there was a significantly greater incidence of grade 3 or 4 myelosuppression in patients with cycle delays or dose reductions than in those without (84% vs 77%, respectively; $P = .013$). Patients with cycle delays or dose reductions received a median of 6 cycles of decitabine compared with those without cycle delays or dose reductions who

received a median of 2 cycles of decitabine. Adverse events, disease progression, lost to follow-up, patient choice, and investigator decision were the main reasons given for patients discontinuing therapy.

In both studies, measurement of hematologic values (hemoglobin, lymphocytes, neutrophils, platelets, and white blood cells) over time showed that the incidence of grade 3 or 4 toxicities was highest in cycle 1 of decitabine therapy then generally decreased over time with subsequent cycles, although all were frequent events, likely a result of the underlying disease. The nadir in hematologic values in cycle 1 was expected from the known myelosuppressive effects of decitabine, and the improvement in mean nadir over successive cycles suggests an absence of cumulative hematologic toxicity.

Effects of Dose Modifications on Response

Patients who had dose modifications, patients who had cycle delays or dose reductions, and patients who had cycle delays had significantly higher ORRs compared with those who had none of these ($P = .015$) (Table III).

There was no significant difference in time to initial dose modification between responding and nonresponding patients. The median time for responders was 2.07 months and the median for nonresponders was 2.10 months.

Effects of Dose Modifications on Survival

Patients who had dose modifications (Figure 1) and patients who had cycle delays or dose reductions (Figure 2) had median OS values similar to those of patients who had neither. Median OS was 16.1 months in patients who had dose modifications and 16.3 months in those who had cycle delays and/or dose reductions compared with 15.3 months and 15.2 months, respectively, in patients who had neither dose modifications nor cycle delays or dose reductions.

Effects of Dose Modification on Transformation to AML

Of the 182 patients in the pooled analysis, 46 (25.3%) underwent transformation to AML. No significant differences were observed in time to AML transformation between patients with and without dose modifications (Figure 3A), and between patients with and without dose delays or dose reductions (Figure 3B).

Predictors of Dose Modifications and Death

Cox regression analysis, including baseline covariates and time-dependent covariates, identified several predictors of decitabine dose modification and death (Table IV). Platelet dependence at baseline was a significant predictor for dose modification ($P = .006$), dose reduction or delay ($P = .011$), and death ($P = .003$). Study effect (DACO-020, 5-day regimen) was also a significant predictor for dose modification and dose reduction or delay ($P < .0001$ in both cases). In addition, IPSS-1 ($P = .002$) and red blood cell dependence at baseline ($P = .0001$) were also significant predictors for death.

DISCUSSION

The findings of this retrospective analysis of a pooled subset of data from patients with MDS enrolled in 2 clinical trials of decitabine suggest that the effects of decitabine dose modification or cycle delay or dose reduction may be beneficial for decitabine response, although no significant effect on patient survival was found. In the pooled analysis, dose modifications, cycle delays or dose reductions, and cycle delays were all associated with a significantly greater ORR compared with no dose modifications of any type. Furthermore, patients with dose modifications had slower progression to AML than patients who had no dose modifications. One hypothesis to explain the effect of decitabine dose modifications on response is that decitabine may act to remove both abnormal and normal rapidly dividing marrow cells during a susceptible phase of the cell cycle; consequently, myelosuppression might be an indicator of decitabine activity.

During the development of decitabine for the treatment of MDS, its dual activity (exhibiting hypomethylation when administered at less intense regimens and cytotoxicity at more intense regimens) [5] led to investigations into alternative dosage regimens. This ultimately led to the approval of a second, 5-day regimen for decitabine administration, in addition to the initially approved 3-day regimen [6]. Based on earlier research and on our own findings, there may be an opportunity for further research to determine whether or not the hypomethylating activity of decitabine can be further enhanced and if responses can be improved by alternate regimens [5].

Our study was limited by its retrospective nature and because it involved a data set pooled from 2 clinical trials with different designs and different decitabine dosage regimens. Thus, specific trial design or physician practice within each trial may have influenced the need for dose modifications or cycle delays or dose reductions. In addition, the fact that patients with dose modifications or cycle delays or dose reductions received a greater median number of cycles of decitabine treatment than those without dose modifications or cycle delays or dose reductions may have biased the results toward better outcomes, as a longer duration of decitabine treatment improves response rates in patients with MDS [12]. Other factors could have contributed to the difference in the number of cycles between patients who did and did not have dose modifications or cycle delays or dose reductions, including the fact that patients were pooled from 2 different studies (each of which had different dose modification rules), or that patients who received only 2 cycles were less able to tolerate treatment.

In conclusion, the results of this retrospective study suggest that dose modifications and on-treatment occurrence of myelosuppression may indicate anti-neoplastic activity with decitabine. These results also suggest that the need for decitabine dose modifications or the development of myelosuppression should not necessarily be interpreted as negative prognostic factors.

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Figure 1. Kaplan-Meier curves for overall survival in patients receiving decitabine with and without dose modifications adjusted for a time-dependent covariate

There was no difference in OS between patients who had dose modifications (median OS, 16.1 months) and those who did not (median OS, 15.3 months).

Figure 2. Kaplan-Meier curves for overall survival in patients receiving decitabine, with and without dose delays or dose reductions adjusted for a time-dependent covariate

There was no difference in OS between patients who had cycle delays or dose reductions (median OS, 16.3 months) and those who had neither (median OS, 15.2 months).

Figure 3. Kaplan-Meier curves for time to AML progression in patients receiving decitabine: (A) with and without dose modifications, and (B) with and without dose delays or dose reductions adjusted for a time-dependent covariate

No significant differences were observed in time to AML transformation between patients with or without dose modifications or between patients with or without dose delays/reductions.

Table I

Patient demographics and baseline characteristics

Characteristic	Study 0007 (N = 83)	Study 020 (N = 99)	Pooled Analysis (N = 182)
Mean age, y (SD)	68.78 (10.45)	70.93 (8.78)	69.95 (9.61)
Sex, n (%)			
Women	28 (34)	28 (28)	56 (31)
Men	55 (66)	71 (72)	126 (69)
IPSS cytogenetic prognostic group, n (%)			
Good	39 (47)	49 (50)	88 (48)
Intermediate	11 (13)	15 (15)	26 (14)
Poor	27 (33)	29 (29)	56 (31)
Unknown	6 (7)	6 (6)	12 (7)
IPSS classification, n (%)			
Low	0 (0)	1 (1)	1 (1)
Intermediate-2	35 (42)	23 (23)	58 (32)
Intermediate-1	26 (31)	52 (53)	78 (43)
High	22 (27)	23 (23)	45 (25)
Type of MDS, n (%)			
De novo	71 (86)	88 (89)	159 (87)
Secondary	12 (15)	11 (11)	23 (13)
Platelets, n (%)			
$<100 \times 10^9/L$	56 (68)	65 (66)	121 (67)
$100 \times 10^9/L$	26 (31)	33 (33)	59 (32)
Missing	1 (1)	1 (1)	2 (1)
ANC, n (%)			
$<1.5 \times 10^9/L$	52 (63)	56 (57)	108 (59)
$1.5 \times 10^9/L$	23 (28)	42 (42)	65 (36)
Missing	8 (10)	1 (1)	9 (5)
Hemoglobin, n (%)			
$<10 \text{ g/dL}$	55 (66)	71 (72)	126 (69)
10 g/dL	22 (27)	28 (28)	50 (28)
Missing	6 (7)	0 (0)	6 (3)
RBC transfusion independent, n (%)	20 (24)	33 (33)	53 (29)
Platelet transfusion independent, n (%)	64 (77)	84 (85)	148 (81)

ANC, absolute neutrophil count; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RBC, red blood cell; SD, standard deviation.

Table II

Patients receiving decitabine who had myelosuppression and required dose modifications

Parameter	Study 0007			Study 020			Study 0007/020		
	n/N (%)	P value*	n/N (%)	n/N (%)	P value*	n/N (%)	P value†	n/N (%)	P value†
Grade 3/4 myelosuppression									
With dose modifications	29/29 (100)		51/75 (68)	NS		80/104 (77)			
Without dose modifications	51/54 (94)	NS	13/24 (54)			64/78 (82)	NS		
With cycle delay/dose reduction	29/29 (100)		47/65 (72)			76/94 (84)			
Without cycle delay/dose reduction	51/54 (94)	NS	17/34 (50)	.003		68/88 (77)	.013		

NS, not significant.

* Chi-square test.

† Cochran-Mantel-Haenszel test (adjusting for study).

Table III
Overall response rate for patients receiving decitabine by subgroups with or without dose modifications

Parameter	ORR Study 0007		ORR Study 020		ORR Study 0007/020	
	n/N (%)	P value*	n/N (%)	P value*	n/N (%)	P value†
Dose modifications						
Yes	7/29 (24)		16/75 (21)		23/104 (22)	
No	8/54 (15)	NS	0/24 (0)	.014	8/78 (10)	.015
Cycle delays or dose reductions						
Yes	7/29 (24)		16/65 (25)		23/94 (24)	
No	8/54 (15)	NS	0/34 (0)	.002	8/88 (9)	.003
Cycle delays						
Yes	5/16 (31)		14/62 (23)		19/78 (24)	
No	10/67 (15)	NS	2/37 (5)	.025	12/104 (12)	.007
Dose reductions						
Yes	2/13 (15)		2/3 (67)		4/16 (25)	
No	13/70 (19)	NS	14/96 (15)	.016	27/166 (16)	NS

n/N, number of responses/number of patients with or without modifications or delays.

ORR, overall response rate; NS, not significant.

* Chi square test.

† Cochran-Mantel-Haenszel Test (adjusting for study).

Table IV

Predictors of dose modification, dose reduction or delay, progression to AML, or death

Parameter	P Value	HR	95% CI
Dose modification			
Study effect (D-0007)	<.0001	0.22	0.14–0.35
Platelet dependence at baseline	.006	2.04	1.22–3.39
Dose reduction or delay			
Study effect (D-0007)	<.0001	0.31	0.20–0.48
Platelet dependence at baseline	.011	2.00	1.17–3.42
Progression to AML			
Study effect (D-0007)	.006	2.42	1.29–4.54
IPSS high	.044	1.97	1.018–3.805
IPSS intermediate-1	.040	0.429	0.192–0.961
Death			
IPSS intermediate-1	.002	0.48	0.31–0.76
Platelet dependence at baseline	.003	1.94	1.25–3.00
RBC dependence at baseline	<.0001	2.46	1.57–3.86

CI, confidence interval; HR, hazard ratio; IPSS, International Prognostic Scoring System; RBC, red blood cell.