Successful treatment of patients with Acute Myeloid Leukemia and Myelodysplastic Syndrome by Decitabine

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Original Article

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ABSTRACT (214 words)

Objectives: The goal of this study was to identify the safety and efficacy of decitabine.

Design: Retrospective study

Setting: Department of Hematology, Ege University Faculty of Medicine

Subjects: Data of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) who treated with decitabine were evaluated retrospectively

Intervention(s): Decitabine administered 20 mg/m^2 by intravenous infusion daily for 5 consecutive days every 4 weeks. The primary end point was overall response rate (ORR). Survival, overall improvement rate (OIR), hematologic improvement (HI), and drug toxicity were analyzed.

Primary Outcome Measure(s): Overall survival (OS), progression-free survival (PFS), ORR, and hematologic adverse event for both AML and MDS, OIR including HI for MDS.

Results: Twenty-five MDS and thirteen AML patients were enrolled. In MDS group, median OS, progression PFS were 21 months and 14 months, respectively. The ORR was 48%, and OIR was 60% which included 12% HI. Seventy-two of patients experienced stable disease or better. For AML, ORR was 46.2%, and median OS, PFS data were not reached due to 76% (n:10) of patients are still alive, and 38% (n:5) of patients have been still receiving treatment. At one year, OS and PFS were 61.4% and 77.8%, respectively.

Conclusion: Decitabine is effective and safe with acceptable toxicity in intermediate and high-risk MDS patients and elderly patients with AML.

KEY WORDS: Administration and dosage, adverse effects, survival analysis

INTRODUCTION

Myelodysplastic syndrome (MDS) is a collection of neoplastic disorders of hematopoietic stem cells characterized by inefficient hematopoiesis, peripheral blood cytopenia, morphologic dysplasia, and susceptibility to acute myeloid leukemia (AML). AML is characterized by the accumulation of immature myeloid 'blasts' in the bone marrow and peripheral blood[1]. MDS and AML lie along a disease continuum with a distinction between the two largely made based upon the blast percentage. In the current World Health Organization (WHO) classification system, blast forms account for at least 20 percent of the total nucleated cells in AML[2]. Gene mutations that affect DNA methylation have been identified in patients with AML. These mutations may result in the expression of genes that are normally silenced or in the silencing of genes that are normally expressed. DNA methylation patterns may also have prognostic significance[3]. Also, 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[4,5]. Decitabine (5-aza-2′-deoxycytidine) is commonly used as a single agent to treat patients with MDS and elderly patients with AML[6]. The drug is a hypomethylating agent that irreversibly inhibits DNA methyltransferase I (DNMT-1) leading to genome-wide global DNA hypomethylation. Decitabine induces leukemic differentiation and re-expression of tumor-associated genes that had been epigenetically silenced[7]. At high doses, cells die from apoptosis triggered by DNA synthesis arrest, and at low doses, cells survive but change their gene expression profile to favour differentiation, reduced proliferation and increased apoptosis. In addition, maximum effects

of DNA hypomethylation have been observed at low doses and with fewer side-effects[8,9]. Decitabine demonstrated promising results in patients with high-risk myelodysplastic syndrome[10,11] and two prospective trials in elderly AML patients had been conducted which showed improved clinical outcomes and acceptable safety profiles compared to conventional treatments[12,13].

SUBJECTS AND METHODS

The study was performed in the Department of Hematology at Ege University Hospital. Following the approval of the study protocol by the local Ethics Committee, data of patients with MDS and AML who treated with decitabine between January 2011 and December 2016 were retrospectively analyzed.

Patients

Eligible patients who were older than 18 years old and diagnosed by MDS or AML according to the 2008 WHO classification enrolled. Patients with MDS were required to have an International Prognostic Scoring System (IPSS) score of ≥0.5.

Study Design

The study was single centered and retrospective. Decitabine was administered as a 20 mg/m^2 intravenous infusion daily for 5 consecutive days (D1-5) every 4 weeks.

All results, except adverse events, for AML and MDS were assessed separately. IPSS and Revised International Prognostic Scoring System (IPSS-R) were used to calculate the risk assessment of MDS. For MDS, age, gender, IPSS and IPSS-R, RAEB 1 or 2 and Eastern Cooperative Oncology Group (ECOG) performance status, cytogenetic classification and, number of decitabine treatment cycles were enrolled. For AML; age, gender, nature (secondary or de novo), blast ratio at the time of diagnosis, ECOG performance status, cycle number were enrolled. Treatment response was assessed by monthly complete blood counts (CBCs) in all patients and bone marrow examination after four cycles in patients except those who underwent allogeneic hematopoietic stem cell transplantation (AHSCT). The timing of bone marrow aspiration biopsy for AHSCT candidates was planned based on improvement in CBCs. The decrease in neutrophil, erythrocyte or platelet was not included in the cytopenia grading system in patients with cytopenia at the beginning of decitabine treatment and was assessed as worsening cytopenia.

Study End Points and Response Assessment

The primary endpoint was the overall response rate (ORR). Secondary end points were hematological improvement (HI) (calculated only for MDS), overall survival (OS), and progression free survival (PFS). In MDS, ORR was assessed by International Working Group (IWG) 2006 response criteria. According to the 2006 IWG criteria, a complete response (CR) is defined as normalization of peripheral blood counts (hemoglobin >11 g/dL without transfusion or erythropoietin use, neutrophils ≥ 1.0 x 10^9/L in the absence of growth factor use, and platelets ≥ 100 x 10^9/L without transfusion or growth factors) and bone marrow blasts less than 5% for at least 4 weeks; marrow complete response (mCR) is defined by ≥ 50% myeloblast reduction from more than 5% myeloblasts to ≤5%, but without recovery of peripheral counts to a level meeting

criteria for CR. Criteria for partial response (PR) are the same as for CR, except for a decrease of ≥ 50% in the percentage of blasts over pretreatment (but still ≥ 5%), or improvement to a less advanced MDS FAB classification than pretreatment. In AML, a CR was defined by ≥ 50% myeloblast reduction from more than 5% myeloblasts to ≤5%, and a PR is defined by the decrease of ≥ 50% in the percentage of blasts over pretreatment (but still ≥ 5%). OS was calculated from the date of the first dose of study drug to the date of death from any cause. PFS 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 the disease.

Statistical analysis

OS, PFS and overall improvement rate (OIR) were calculated using Kaplan-Meier product-limit estimates, along with 95% confidence interval (CI). Survival data of patients who underwent AHSCT were not included into the survival data of patients with MDS and AML.

RESULTS

Results for MDS

The median age was 67 years (23 – 82 years), female to male ratio was 44% to 56%, and patients with MDS RAEB-1 and RAEB-2 were 44% and 56%, respectively. Patients with IPSS intermediate-1 were 32%, and patients with IPSS intermediate-2 or high were 48% and all patients had ECOG performance score less than 3. IPSS and R-IPSS scores of 20% of patients couldn't be calculated because their cytogenetics were not reached (Table 1).

Treatment response

Twelve of the 25 patients experienced CR (12%), mCR (32%), or PR (4%); ORR, which included CR+PR+mCR was found to be 44%. OIR was found to be 60%, which included ORR plus HI. 72% of patients experienced stable disease or better (Table 2).

HI was detected at the end of median 2 cycles. Best results were observed in hemoglobin levels as 32%, following by platelets as 16% improvement. HIs were observed in 44% of all MDS patients (Table 3). Median OS was 38 months in patients with MDS who achieved HI, whereas it was 11 months in patients who couldn't achieve HI. This finding was not statistically significant (p: 0.288, p> 0.05).

When we assessed according to IPSS score, response rates of IPSS with intermediate 1 and IPSS with 2 or high were observed to be quite similar to each other (ORR %50 vs %41.6, OIR 62.5% vs. 58.3% respectively) (Table 4).

OS in 1, 2 and 5 years were 62%, 47% and 17% respectively. PFS 1, 2 and 5 years were 54%, 45% and 30% respectively (Table 5). Median OS was 21 months (95% CI: 0 – 46.153) and median PFS was 14 months (95% CI: 0 – 37.308), as shown in Figure 1. The OS and PFS outcomes of patients who achieved response (CR+mCR+PR) were observed to be statistically significantly better than the others ($p<0.013$ and $p<0.005$, respectively), as shown in Figs 2a and 2b. The OS and PFS of patients who couldn't achieve response were 11 and 8 months, respectively.

Results for AML

The median age was seventy-five years (range: 18 – 81 years) and the female to male ratio was 7 to 6. Three patients had secondary, and 10 patients had de novo AML. The median blast was 70% (range 25% - 95%) at the time of diagnosis, and they received a median two cycles of treatment (range 1-10). All patients had an ECOG performance score of less than 3. The patient's characteristics are summarized in Table 6.

Treatment response

Eight patients were evaluated by bone marrow examination to determine treatment response. The treatment response could not be evaluated in five patients; until completion of the fourth cycle of treatment, three patients died, and two patients discontinued decitabine treatment because of an inadequate hematologic response of peripheral blood and poor performance status. In this trial, CR and PR were observed in four and two patients, respectively. As a result, six of thirteen AML patients experienced CR (n:4) or PR (n:2), and ORR was found as 46%. Two patients couldn't achieve a response. All six patients who achieved response had de novo AML. Median OS and PFS rates were not reached due to 76% of the patients (n: 10) were alive, and 38% of the patients' treatment continued (n: 5). One year PFS and OS were observed 77.8% ± 13.9 and 61.4% ± 19.7, respectively.

Hematologic adverse events

Hematologic toxicity was observed in half of the patients and grade 3 - 4 hematological toxicity was observed in 39% of patients (Table 7). 33% febrile neutropenia, 36% grade 3 - 4 neutropenia and 13% grade 3 - 4 thrombocytopenia were observed. The drug mostly caused neutropenia. Neutropenic fever was observed in one-third of patients.

Seven of twenty-five MDS and one of thirteen AML patients underwent to AHSCT. Six of seven MDS and one AML patients achieved CR before transplantation. They received a median 3 cycles of decitabine, and responses were detected by the end of a median 3 cycles.

Comparison of the current study with previous reports in MDS

We compared our results with three previously reported data using a 5-day regimen (20 mg/m^2/d or 15 mg/m^2/day, Table 8)[14-16].

DISCUSSION

In the current study, we retrospectively analyzed 25 elderly patients with MDS. The effectiveness of decitabine in MDS has been reported from several clinical trials. To evaluate the efficacy of decitabine in MDS, we compared our results to the data of the previous trials. In these trials, ORR (CR+mCR+PR) were reported between 32% - 58%[10,14-18]. ORR in our study was better than the results of two trials mentioned in table 8 (48% vs. 32%, 36.7% respectively). This could be attributed mainly to the patient characteristics with the absence of patients with chronic myelomonocytic leukemia (CMML) in our patient group. ORR result in decitabine of reduced dosage in Chinese patients' trial was better than our ORR result (58.2% vs. 48%); this may be due to younger median age in that trial (60 y vs. 67 y) (Table 8). The OS and PFS outcomes of

patients who achieved overall response were observed statistically significantly better than the others (Fig 2).

Our study showed similar CR rates as reported by ADOPT and DIVA trials (12% vs. 17% and 12.9% respectively). Low CR ratios can be associated with suppression of normal hematopoiesis in MDS. So, it is natural that a substantial proportion of patients show mCR without complete blood count recovery after successful treatment with decitabine.

OIR result in our study, which contain 32% of MDS patients with IPSS Int-1 risk was better than results of ADOPT and DIVA trials which contains over 50% of MDS patients with IPSS Int-1 risk (OIR; 60% vs 51% and 55.4%). Similarly, OIR (67.1%) of retrospective trial in Chinese patients which contained 67.1% of MDS patients with IPSS Int-2 was better than the results of ADOPT and DIVA trials. We can say that decitabine is more effective in patients with Int 2 or high (Table 8). However, when we assessed according to IPSS score in our study; OIR of IPSS with int- 1, int-2, or high were observed quite similar to each other (OIR; 62.5% vs 58.3% respectively).

In our study, the achievement of HI was associated with prolonged OS (Median OS; 38 months in whom achieved HI vs 11 months in whom couldn't achieved HI). A previous study reported that HI was a significant predictor of OS [16]. Although our finding was not statistically significant (p: 0.288, p> 0.05), decitabine treatment might prolong survival in patients achieving HI.

Although it is not a head-to-head comparison, the median OS in our study was slightly better than the results of three trials mentioned in table 8 (21 months vs 19.4, 18 and 17.7 months, respectively). This could be attributed mainly to the patient characteristics with the absence of patients with CMML in our patient group and prolonged treatment up to 32 cycles or higher mCR rate in our study (32% vs. 15%, 27.8% and 22.8%). The clinical importance of mCR is uncertain[14], but it may be of value in prolonged survival. Another importance of mCR will be bridging to marrow transplantation where decitabine may induce rapid myeloblast reduction before initiation of transplant conditioning regimens, with less risk than with more intensive approaches. In our study 6 of 7 patients with MDS who underwent AHSCT achieved mCR before transplantation.

AML is the most common acute leukemia in adults and accounts for approximately 80 percent of adult leukemia cases[19]. In adults, the median age at diagnosis is around 65 years. However, the treatment options for the elderly AML patients have been limited and they usually show poor clinical outcomes owing to their unfavorable cytogenetics poor performance, comorbidity or prior hematologic neoplasms[20]. As a result, a substantial portion of the patients is not suitable for intensive treatment. Our results in AML were limited. In the present study, we retrospectively analyzed 13 elderly patients with AML. Decitabine was well tolerated and patients with AML received a median of 2 cycles of treatment. A subsequent phase III trial named DACO-016 was carried out in 485 patients with AML of intermediate or poor-risk cytogenetics older than 65 years and they were randomized to receive either decitabine or physician's choice. With the median age of the patients being 73 years and median four cycles, the response rate was also higher in decitabine arm, as it was associated with a significantly higher rate (17.8% vs. 7.8%, respectively, p = 0.001)[13]. In our study, approximately half of patients with AML (ORR 46%) experienced CR or PR with decitabine. In a retrospective multicentre study, eighty Korean patients with AML were enrolled with the median age of patients being 73

years, and 35 of them underwent bone marrow examination after median 3 cycles reported that 10 of 35 patients (28.5%) achieved response and 1-year survival rate was 38.3%[21]. Higher ORR could be associated with a limited number of patients, a lack of cytogenetic status before decitabine treatment, and also single-center study. In another retrospective single-center study, twenty-four patients with newly diagnosed AML were enrolled. They reported that 12 of 17 patients achieved a response[22]. Similarly, in our study 6 of 8 patients who underwent bone marrow examination for response assessment achieved a response. Median OS was not reached due to ten of thirteen patients were alive.

Besides, in our study, patients didn't use antibacterial prophylaxis during treatment, and neutropenic fever was observed in one-third of them. So antibacterial prophylaxis to prevent infectious complications can be a reasonable approach due to decitabine mostly caused neutropenia, and HI was observed at least in neutrophils as we reported in our study.

The current study has several limitations. Data were collected in a retrospective manner and from a single center. In MDS, the IPSS score couldn't be calculated in 20% of patients due to unknown karyotype tests before the treatment. Cytogenetic response to decitabine treatment in patients with MDS couldn't be assessed due to a lack of the genetic tests in bone marrow examination of response assessment.

In AML, we couldn't reach the cytogenetic and molecular tests. So, we don't know risk assessment before the treatment but in the real-world situation, there is no known effective treatment in patients with AML who cannot tolerate intensive chemotherapy with poor performance status.

CONCLUSION

Decitabine was well tolerated in both groups. The response to decitabine treatment was found to be associated with a survival benefit in MDS patients. While the treatment options for elder AML patients have been limited, our real-world data suggest that decitabine could be an effective treatment of choice. As a result, decitabine is effective and safe with acceptable toxicity in intermediate or high-risk MDS patients and elderly patients with AML.

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Contributions:

H. B: writing and editing the manuscript

E.A.D: editing the manuscript, collecting data

F.D.A: collecting data

Y.U: writing and editing the manuscript

N.S: collecting data

G.S: convincing the idea

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FIGURE LEGENDS

Fig 1: Median OS and PFS were 21 and 14 months respectively

Fig 2a: OS in CR+mCR+PR

Fig 2b: PFS in CR+mCR+PR

Table 1: Patient characteristics for MDS at baseline

Patient Characteristic	**% (n)**
Median Age [years]	67 [23-82]
Gender (Female/Male)	44/56% (n: 11/14)
MDS RAEB-1	44% (n:11)
MDS RAEB-2	56% (n:14)
IPSS intermediate 1	32% (n:8)
IPSS intermediate 2 or high	48% (n:12)
IPSS unknown (N/A)	20% (n:5)
R-IPSS intermediate	20% (n:5)
R-IPSS high or very high	56% (n:14)
Cytogenetic classification of risk Intermediate Poor Unknown	 64% (n:16) 16% (n:4) 20% (n:5)
ECOG performance status (0-2) ECOG 0 ECOG 1 ECOG 2	100% (n:25) 24% (n:6) 64% (n:16) 12% (n:3)
Median cycle	4 cycles [1-32]

MDS: Myelodysplastic syndrome, ECOG: Eastern Cooperative Oncology Group performance status, N/A: not assessed, IPSS: International Prognostic Scoring System, R-IPSS: Revised International Prognostic Scoring System, RAEB: refractory anemia with excess blasts, n: number of patients

Table 2: Treatment Response to Decitabine in MDS patients

Response Assessment		**No of Patients (%)**	
CR		3 (12)	
mCR		8 (32)	
	mCR with HI		5
	mCR without		3
PR		1 (4)	
HI only		3 (12)	
SD		3 (12)	
PD		3 (12)	
Not Assessable		4 (16)	
Overall complete response rate, CR+mCR		11 (44)	
Overall response rate, CR+mCR+PR		12 (48)	
Overall improvement rate, CR+mCR+PR+HI		15 (60)	
Rate of stable disease or better, CR +mCR + PR + HI + SD		18 (72)	

IWG: International Working Group, CR: complete response, mCR: Marrow CR, PR: Partial response, HI: Hematologic improvement, SD: Stable disease, PD: Progressive disease.

mCR: A total of 4 patients were not assessable for a response assessment because post-therapy bone marrow and/or CBC values were not available.

Table 3: HIs were detected at the end of median two cycles

HI	No of Patients	%
HI-Neu	2	8
HI-E	8	32
HI-PLT	4	16
Total	11	44

HI: Hematologic improvement, Neu: Neutrophil, E: Erythroid, PLT: Platelets

Table 4: Response results according to IPSS scores

Response assessment	Intermediate 1 n:8	Intermediate-2 or high n: 12
CR+mCR n (%)	4 (50)	4 (33.3)
PR n (%)	-	1 (8.3)
SD n (%)	1 (12.5)	2 (16.6)
HI (total) n (%)	4 (50)	6 (50)
HI (only) n (%)	1 (12.5)	2 (16.6)
OIR n (%)	5 (62.5)	7 (58.3)
PD n (%)	1 (12.5)	2 (16.6)
N/A %	12.5	8.3
ORR %	50	41.6

mCR: Marrow CR, PR: Partial response, SD: stable disease, HI: Hematologic improvement, OIR: Overall improvement rate, PD: Progressive disease, N/A: Not assessed, ORR: Overall response rate, IPSS: International Prognostic Scoring System, n:number of patients

Table 5: 1, 2 and 5-year OS and PFS

Survival	**1 year**	**2 year**	**5 year**
OS	62.9%±12.2	47.1%±13.3	17.7%±14.4
PFS	54.9%±13.9	45.8%±13	30.5%±15.4

OS: Overall survival, PFS: Progression free survival

Table 6: Patient characteristics for AML

Patient Characteristic at baseline	
Median Age (years)	75 (18-81)
Gender: Female/Male	n: 7/6
Secondary	n: 3
De novo	n: 10
Median cycle	2 cycles (1-10)
ECOG 0-2	n:13
ECOG 0	n:3
ECOG 1	n:4
ECOG 2	n:6
Initial median blast ratio	70% (25-95)

n: number of patients

Table 7: Hematologic toxicity

Grade	**Neutropenia n (%)**	**Thrombocytopenia n (%)**	**Anemia n (%)**
Grade 1	_	3 (7.9)	_
Grade 2	1 (2.6)	_	_
Grade 3	7 (18.4)	2 (5.3)	_
Grade 4	7 (18.4)	3 (7.9)	_
Grade 3-4	14 (36.8)	5 (13.2)	_
Worsening of cytopenias	10 (26.3)	10 (26.3)	23 (60.5)

Hematologic toxicity was observed in 50% of patients (n: 19). Grade 3-4 hematological toxicity was observed in 39% of patients (n: 15) n:number of patients

Table 8: Comparison previous trials and the current study

Variable Parameters	**Current Study**	**ADOPT**	**Decitabine of Reduced Dosage in Chinese Patients**	**DIVA study**
No of patient	25	99	79	101
Study design	Retrospective	Prospective	Retrospective	Prospective
Median age, years	67 (23-82)	72 (34-87)	60 (28-82)	65 (23-80)
Eligibility	WHO (IPSS ≥0.5)	FAB MDS (IPSS ≥0.5)	FAB MDS (IPSS ≥0.5)	WHO(IPSS≥0.5)+ CMML
IPSS intermediate 1	32%	54%	32.9%	52%
IPSS intermediate 2 or high	48%	46%	67.1%	48%
Unknown	20%	-	-	-
Cytogenetic classification of risk				
Good	0 %	49%	50.6%	64.3%
Intermediate	64%	15%	24.1%	14.8%

Poor	16%	26%	25.3%	18.8%
Unknown	20%	6%	-	-
Decitabine regimen	20 mg/M2/dx5 d	20 mg/M2/dx5 d	15 mg/M2/dx5 d	20 mg/M2/dx5 d
Courses, median (range)	4 (1–32)	5 (1–17)	4 (1-11)	5 (1–18)
Treatment response				
CR	12%	17%	29.1%	12.9%
mCR	32%	15%	27.8%	22.8%
PR	4%	0 %	1.3%	1%
HI	12%	18%	8.9%	18.8%
SD	12%	24%	6.3%	10.9%
PD	12%	10%	26.6%	7%
Overall complete response rate(CR+mCR)	44%	32%	56.9%	35.7%
Overall response rate, CR+mCR+PR	48%	32%	58.2%	36.7%
Overall improvement rate (CR+mCR+PR+HI)	60%	51%	67.1%	55.4%
Rate of stable disease or better (CR +mCR + PR + HI + SD)	72%	75%	73.4%	66.3%
Overall survival				
Median	21 months	19.4 months	18 months	17.7 months
1-year probability	62.9%	66%	63.3%	78.6%

IWG: International Working Group, CR: Complete response, mCR: Marrow CR, PR: Partial response, HI: Hematologic improvement, SD: Stable disease, PD: Progressive disease, WHO MDS: Myelodysplastic syndrome defined by the World Health Organization classification, IPSS: International Prognostic Scoring System, CMML: Chronic myelomonocytic leukemia, FAB MDS: MDS defined by French-American-British classification