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A comparison of toxicities in acute myeloid leukemia patients with and without renal impairment treated with decitabine

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Abstract

Purpose: There are limited data regarding the clinical use of decitabine for the treatment of acute myeloid leukemia in patients with a serum creatinine of 2 mg/dL or greater.

Methods: We retrospectively evaluated 111 patients with acute myeloid leukemia who had been treated with decitabine and compared the development of toxicities during cycle 1 in those with normal renal function (creatinine clearance greater than or equal to 60 mL/min) to those with renal dysfunction (creatinine clearance less than 60 mL/min).

Results: Notable differences in the incidence of grade ≥3 cardiotoxicity (33% of renal dysfunction patients vs. 16% of normal renal function patients, $p = 0.042$) and respiratory toxicity (40% of renal dysfunction patients vs. 14% of normal renal function patients, $p = 0.0037$) were observed. The majority of heart failure, myocardial infarction, and atrial fibrillation cases occurred in the renal dysfunction group. The odds of developing grade ≥3 cardiotoxicity did not differ significantly between patients with and without baseline cardiac comorbidities (OR 1.43, $p = 0.43$).

Conclusions: This study noted a higher incidence of grade ≥3 cardiac and respiratory toxicities in decitabine-treated acute myeloid leukemia patients with renal dysfunction compared to normal renal function. This may prompt closer monitoring, regardless of baseline cardiac comorbidities. Further evaluation of decitabine in patients with renal dysfunction is needed.

Keywords

Decitabine; acute myeloid leukemia; renal impairment; toxicity

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Declaration of Conflicting Interests

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Introduction

Standard induction chemotherapy for patients with newly diagnosed acute myeloid leukemia (AML) who have been deemed fit to receive a high intensity regimen typically includes an anthracycline in combination with cytarabine. However, given that 67 is the median age at diagnosis, older patients and those with significant comorbidities or reduced performance status are more likely to experience excessive toxicity with high-intensity therapy without receiving benefit.[1] For these patients, the development of lower intensity regimens that effectively treat AML is needed. The hypomethylating agents, decitabine and azacitidine, are lower intensity treatment options for elderly or unfit patients with AML who either refuse or are not candidates for standard induction chemotherapy.[2] At The Ohio State University, decitabine is the hypomethylating agent of choice for AML. Phase II and III studies evaluating decitabine 20 mg/m^2 intravenously daily for five days of a four-week cycle reported complete remission (CR) rates of 24% and 17.8%, respectively.[3,4] Blum et al. evaluated decitabine 20 mg/m^2 intravenously daily for 10 days of a four-week cycle in patients aged 60 years or older with newly diagnosed AML and observed a CR rate of 47%. Interestingly, the CR rate was highest at 82% among patients with complex karyotype AML. [5] Given that the remission rates achieved in this study were comparable to those observed following induction chemotherapy with cytarabine and an anthracycline in this age group, the use of decitabine as an alternative regimen has become an option for those unable to tolerate intensive therapy.

With respect to its proposed mechanism of action, decitabine is a deoxyribose derivative of azacitidine that inhibits DNA methylation and thus affects gene expression. By inhibiting methylation in DNA regions responsible for the development of malignancies, hypomethylating agents prevent growth and promote apoptosis of malignant cells.[6] In phase I trials, the elimination half-life of decitabine was found to be approximately 35 min with a total urinary excretion of less than 1%.[7] However, the full pharmacokinetic profile of this agent has yet to be fully described. Decitabine does appear to be broken down into several unknown products that may contribute to its toxic effects, and the exact elimination route of these byproducts is unknown.[8]

Based on current prescribing information for its labeled indication of myelodysplastic syndromes (MDS), decitabine has not been studied in patients with a serum creatinine of 2 mg/dL or greater, and it is suggested that it should be used with caution.[7] The studies evaluating decitabine use in AML either excluded patients with a serum creatinine of greater than or equal to 1.5 mg/dL or patients with a creatinine clearance (CrCl) of less than 40 mL/min.[4,9] As a result, there are limited data regarding the use of decitabine for the treatment of hematologic malignancies in patients with renal impairment. In a retrospective study of patients with AML, MDS, and chronic myelomonocytic leukemia, Batty et al. demonstrated an increased need for dose interruptions, dose reductions, and treatment delays for decitabine and azacitidine in patients with renal impairment, defined as CrCl ≤ 59 mL/min. [10]

Given the limited reported data on the use of decitabine in patients with renal impairment, there is a need to evaluate whether this could play a role in the development of toxicities in patients receiving this agent for the treatment of AML. The purpose of this study is to compare the development of toxicities in patients with normal renal function and renal dysfunction during cycle 1 of therapy with decitabine for AML.

Materials and methods

Patients

We collected clinical data on patients ≥18 and <90 years of age with newly diagnosed or relapsed AML who received at least one cycle of decitabine therapy between 1 January 2010 and 31 July 2014 at The James Cancer Hospital at The Ohio State University. The clinical scientific review committee and institutional review board at The Ohio State University reviewed and approved the protocol for our study.

Study design

This was a retrospective cohort study comparing the toxicities that occurred during cycle 1 of decitabine for the treatment of AML. Patients were placed into one of two groups based on creatinine clearance calculated using Cockcroft and Gault: CrCl ≥ 60 mL/min or CrCl < 60 mL/min. Serum creatinine values were collected on the start date of treatment. Creatinine clearance was calculated utilizing ideal body weight (IBW) if actual body weight (ABW) was within 120% of IBW, ABW if ABW was less than IBW, or adjusted body weight if ABW was greater than 120% of IBW. Adjusted body weight was defined as IBW with the addition of 40% of the difference between ABW and IBW. Patients received decitabine 20 mg/m^2 intravenously daily for 10 days of every 28-day cycle.[5] We collected baseline demographic data including disease type, age, gender, performance status, Hematopoietic Stem Cell Transplant Comorbidity Index (HCT-CI), previous anthracycline therapy, and renal function.[11] Non-hematologic adverse events possibly related to decitabine as per the package insert were collected and are listed in Table 1.[7] Literature-reported incidence of each adverse event is included. These literature-reported values are based on decitabine 20 mg/m^2 daily for five days of a 28-day cycle, which is lower than the dose used in our patient population. Adverse events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). We also assessed the need for dose adjustments for cycle 2 or discontinuation of therapy in each group, 30-day mortality, and hospital length of stay for patients that required hospitalization for complications.

Statistical analysis

In this study, cardiovascular, central nervous system, dermatologic, endocrine, gastrointestinal, hepatic, infectious, neuromuscular, and respiratory toxicities were compared between AML patients with normal renal function and renal dysfunction. Categorical variables were presented as frequencies and percentages while continuous variables were presented as medians and the interquartile range (IQR). Categorical variables were analyzed using Fisher's exact tests; continuous variables were analyzed using Mann–Wilcoxon–Whitney rank tests since the distributions of these variables were deviated from normal

distributions. Similar analyses were applied on secondary outcomes, such as mortality, hospitalization, dose delay, dose discontinuation, and hospital length of stay along with patient demographics and clinical characteristics. The odds of developing grade ≥ 3 cardiotoxicity in these two groups of patients were analyzed using Cochran–Mantel–Haenszel tests. All statistical tests were two sided, and values of $p < 0.05$ were regarded as statistically significant. The statistical software, R3.2.0 (R Foundation for Statistical Computing) was used in this study.

Results

Patients

A total of 111 decitabine-treated patients with AML were included in this study. Sixty-three patients had a baseline CrCl ≥ 60 mL/min (normal renal function) and 48 patients had a baseline CrCl < 60 mL/min (renal dysfunction). Table 2 summarizes the patient characteristics. The majority of patients had de novo AML (62% in the normal renal function group and 64% in the renal dysfunction group). Baseline characteristics, including gender, disease type, ECOG performance status, prior anthracycline therapy, and HCT-CI were similar between the groups. Patients in the renal dysfunction group were significantly older than patients in the normal renal function group (73 vs. 68, $p < 0.001$). The median baseline serum creatinine and CrCl in the normal renal function group were 0.8 g/dL and 83 mL/min, respectively. In contrast, the median baseline serum creatinine and CrCl in the renal dysfunction group were 1.1 g/dL and 46 mL/min, respectively. Patients with severe renal dysfunction (CrCl < 30 mL/min) ($n = 5$) had a significantly higher median baseline serum creatinine of 3.8 g/dL compared to the median of the rest of the patients in the renal dysfunction group (1.08 g/dL, $n = 43$, $p < 0.001$). One patient had chronic kidney disease on hemodialysis (HD) and one patient had acute kidney injury on chronic kidney disease on continuous renal replacement therapy (CRRT) at the time of decitabine initiation.

Toxicity

All grade non-hematologic toxicities are described in Tables 3 and 4. Differences were noted in the central nervous and cardiac organ systems. More specifically, central nervous system toxicity of all grades occurred more frequently in patients with renal dysfunction as compared to patients with normal renal function (90% vs. 73%, $p = 0.033$). Dizziness was the main toxicity driving this difference (27% vs. 11%, $p = 0.045$). Any grade cardiovascular toxicity was not significantly different, but more patients in the renal dysfunction group developed tachycardia during treatment (13% vs. 2%, $p = 0.041$).

Grade ≥ 3 non-hematologic toxicities are described in Tables 3 and 4. The most pronounced differences in grade ≥ 3 toxicities between the two groups were in respiratory and cardiovascular toxicities. Patients with renal dysfunction experienced grade ≥ 3 respiratory toxicity significantly more frequently than those with normal renal function (40% vs. 14%, $p = 0.0037$). There were trends toward more hypoxia (23% vs. 10%, $p = 0.065$) and respiratory failure (15% vs. 5%, $p = 0.097$) in the respiratory dysfunction group compared to the normal renal function group. Not surprisingly, the majority of cases of respiratory failure occurred concomitantly with lung infections. There was a trend towards greater incidence of lung

infections in the renal dysfunction group compared to the normal renal function group (29% vs. 14%, $p = 0.063$). Similarly, grade ≥ 3 cardiovascular toxicities occurred more frequently in patients with renal dysfunction compared to those with normal renal function (33% vs. 16%, $p = 0.042$). All cases of grade ≥ 3 heart failure ($n = 4$) and myocardial infarction ($n = 2$), as well as three of the four cases of atrial fibrillation occurred in the renal dysfunction group. Three of the four heart failure cases and two of the three atrial fibrillation cases were new onset. All cases of atrial fibrillation occurred in the setting of acute infection. Both patients that developed myocardial infarction had a history of coronary artery disease. The incidence of heart failure was significantly higher in the renal dysfunction group (8.3% vs. 0%, $p = 0.033$).

Due to the differences in the incidence of cardiac toxicity between the groups, we assessed each patient for baseline cardiac comorbidities, including arrhythmia, coronary artery disease/myocardial infarction, and congestive heart failure. The percentage of patients with baseline cardiac comorbidities was similar between the normal renal function group (43%) and renal dysfunction group (44%). Figure 1 shows the percentage of patients who developed grade ≥ 3 cardiotoxicity based on the presence or absence of cardiac comorbidities and renal function group. Grade ≥ 3 cardiotoxicity occurred more frequently in patients with renal dysfunction and cardiac comorbidities (38%) than those with normal renal function and cardiac comorbidities (19%). These percentages were slightly lower in both renal function groups for patients without cardiac comorbidities (30% in the renal dysfunction group and 14% in the normal renal function group). Despite these differences, the odds of developing grade ≥ 3 cardiotoxicity in the presence of cardiac comorbidities compared to the absence of cardiac comorbidities at baseline were not significant (OR 1.43, 95% CI 0.59–3.45, $p = 0.43$). There were, however, significantly higher odds of developing grade ≥ 3 cardiotoxicity in the presence of renal dysfunction compared to normal renal function (OR 2.65, 95% CI 1.07–6.54, $p = 0.033$).

Five patients in this study had severe renal dysfunction, characterized by a CrCl < 30 mL/min, with two patients requiring dialysis (one was receiving HD and one was receiving CRRT). Four of these five patients experienced cardiac toxicity, all of which were grade 3 or 4, and included hypotension in the setting of sepsis, hypertension, and atrial fibrillation. Two of these four patients had underlying cardiac comorbidities, including heart failure and atrial fibrillation. Four of the five patients were hospitalized during cycle 1 for toxicity, and two of these patients died within 30 days: one due to sepsis and one due to respiratory failure. The other two hospitalized patients were admitted for febrile neutropenia within 30 days of initiation of therapy.

Mortality, hospitalizations, and treatment delays

The outcomes of the secondary endpoints are provided in Table 5. Among the secondary study objectives, 30-day all-cause mortality differed between the groups (6.3% in normal renal function vs. 20.8% in renal dysfunction, $p = 0.041$). The causes of death in the normal renal function group were sepsis in three patients and leukemia in one patient. In the renal dysfunction group, death was due to sepsis (two patients), respiratory failure (five patients), and leukemia (three patients). About half of the patients in both groups were hospitalized

during cycle 1 due to toxicities ($p = 0.57$). The median length of stay for patients requiring hospitalization was similar between the groups (seven days in normal renal function group vs. eight days in renal dysfunction group, $p = 0.41$). More patients in the normal renal function group were delayed for cycle 2 due to toxicity (17.5% in normal renal function group vs. 8.3% in renal dysfunction group, $p = 0.26$), while more patients in the renal dysfunction group discontinued decitabine after cycle 1 (9.5% in normal renal function group vs. 16.7% in renal dysfunction group, $p = 0.38$); however, these were not statistically significantly different. Febrile neutropenia was the most common toxicity leading to cycle 2 delays.

Discussion

This study demonstrates differences in toxicities following one cycle of decitabine in AML patients with renal dysfunction as compared to normal renal function. It is difficult to determine whether the toxicities were related to decitabine, the disease process of AML, acute infection, or another confounding factor in this high risk group of patients. The patients in the renal dysfunction group were significantly older than those without renal dysfunction, which may have impacted tolerability and toxicity development ($p < 0.001$). Older patients are more likely to have comorbidities and worse performance status, increasing the risk for adverse events. Interestingly, the greatest differences in toxicities between the groups were found to be cardiotoxicity and respiratory toxicity. Indeed, cardiac toxicity was the most clinically relevant adverse event as the majority of cases of grades 3 and 4 atrial fibrillation, heart failure, and myocardial infarction occurred in the renal dysfunction group. This suggests that this particular group of patients may be at increased risk for the additional cardiac events while on therapy regardless of baseline cardiac comorbidities and that closer monitoring may be needed.

When comparing the occurrence of pulmonary and cardiac toxicities in our study to previous studies of decitabine in AML patients with normal renal function, several differences are noted. The rates of grade ≥ 3 pneumonia have been reported as 11–21% in studies of decitabine 20 mg/m^2 daily for five days.[3,4] Our grade 3 or higher pneumonia rate in the normal renal function group was comparable at 14%; however, in the renal dysfunction group, this rate was higher at 29%. With respect to cardiac toxicity, Blum et al. noted grade ≥ 3 decreased left ventricular ejection fraction in 2% of their patients on the 10-day regimen, which was comparable to the 0% observed in our normal renal function group.[5] However, our study identified 6.25% of patients in the renal dysfunction group with grade ≥ 3 heart failure that was new. Blum's study also reported grade ≥ 3 arrhythmia in 6% of patients, similar to our findings.[5] Lastly, with respect to grade ≥ 3 sepsis, rates of 4.8–6% have been reported in patients treated with the five-day schedule.[4,9] Our rates were higher, even in the normal renal function group, with 17% of patients in the normal renal function group and 19% of the renal dysfunction group experiencing grade ≥ 3 sepsis. Based on these comparisons, our renal dysfunction group experienced more grade 3 or higher pneumonia, heart failure, and sepsis than patients with normal renal function in previously reported studies of decitabine. However, most of these studies, with the exception of Blum's study, assessed the five-day decitabine regimen as opposed to the 10-day decitabine regimen utilized in our study.

Differences were also noted between the groups in the secondary endpoints of 30-day all cause mortality and decitabine dose delays and discontinuations. Death from sepsis occurred similarly in both groups, and only slightly more patients in the renal dysfunction group died of their leukemia. Death from respiratory failure occurred exclusively in the renal dysfunction group (five patients), all of whom had concomitant pneumonia at the time of respiratory failure. This may be explained by the trend towards greater development of respiratory failure in the renal dysfunction group. The higher incidence of decitabine discontinuation in the renal dysfunction group but higher rate of dose delay in the normal renal function group is likely due to the development of more severe toxicities in the renal dysfunction patients that required discontinuation rather than a dose delay.

Several factors that were not assessed in this study may have contributed to the results. Only cardiac comorbidities were assessed in this study; however, the presence of additional organ dysfunction could also affect the development of toxicities. Whether disease-specific characteristics (e.g. presenting white blood cell count, lactate dehydrogenase, cytogenetics) place patients at higher risk for toxicities was not assessed but could also play a role. For example, patients with relapsed or refractory disease may be more heavily pretreated with other chemotherapeutic agents, which may predispose them to more adverse events with subsequent lines of treatment. This is particularly true for refractory disease that requires further treatment very soon after completing first-line chemotherapy. Further assessment of these potential confounding factors would help to determine the true magnitude of the effect of renal function on the development of toxicities.

Our study has several limitations. Data collection was dependent on accurate charting in the medical record of toxicities and severity for CTCAE grading. Data were collected for only one cycle of therapy, which did not allow for a complete assessment of toxicities or the evaluation of efficacy outcomes such as response rate or survival. This study included a heterogeneous group of both newly diagnosed as well as relapsed AML patients, which, as noted previously, may have increased the likelihood that this cohort of patients would develop toxicities from treatment. The groups were determined based on baseline renal function, and did not take into account fluctuations in serum creatinine or development of acute kidney injury during cycle 1 of therapy. As a result, patients whose renal function deteriorated during cycle 1 of treatment may have been assessed in the normal renal function group despite their decrease in renal function. Finally, the toxicities chosen for data collection in this study came from the decitabine prescribing information; however, it is difficult to discern whether or not these toxicities are solely the result of decitabine therapy due to the retrospective nature of this study and the possibility that these toxicities could have been caused by the AML disease process itself or other patient characteristics.

In conclusion, we noted a higher incidence of grade ≥ 3 cardiac and respiratory toxicities in decitabine-treated AML patients with renal dysfunction compared to those with normal renal function. Due to the limitations of this study, we cannot conclude that this is a result of decitabine use in renal dysfunction, but it may prompt closer monitoring, including telemetry and echocardiogram assessments, for patients with severe renal dysfunction undergoing AML treatment with decitabine.

Future studies to investigate the correlation between renal dysfunction and increased toxicities with decitabine and to identify dosing strategies in this patient population are needed. This could be accomplished by expanding the analysis of decitabine toxicity to patients with severe renal dysfunction (CrCl < 30 mL/min), assessment after more than one cycle of decitabine, and the inclusion of efficacy endpoints such as response and survival. Most importantly, further assessment of decitabine dose reduction techniques based on pharmacokinetic data would provide treatment strategies to reduce toxicity while optimizing response in patients with renal dysfunction.

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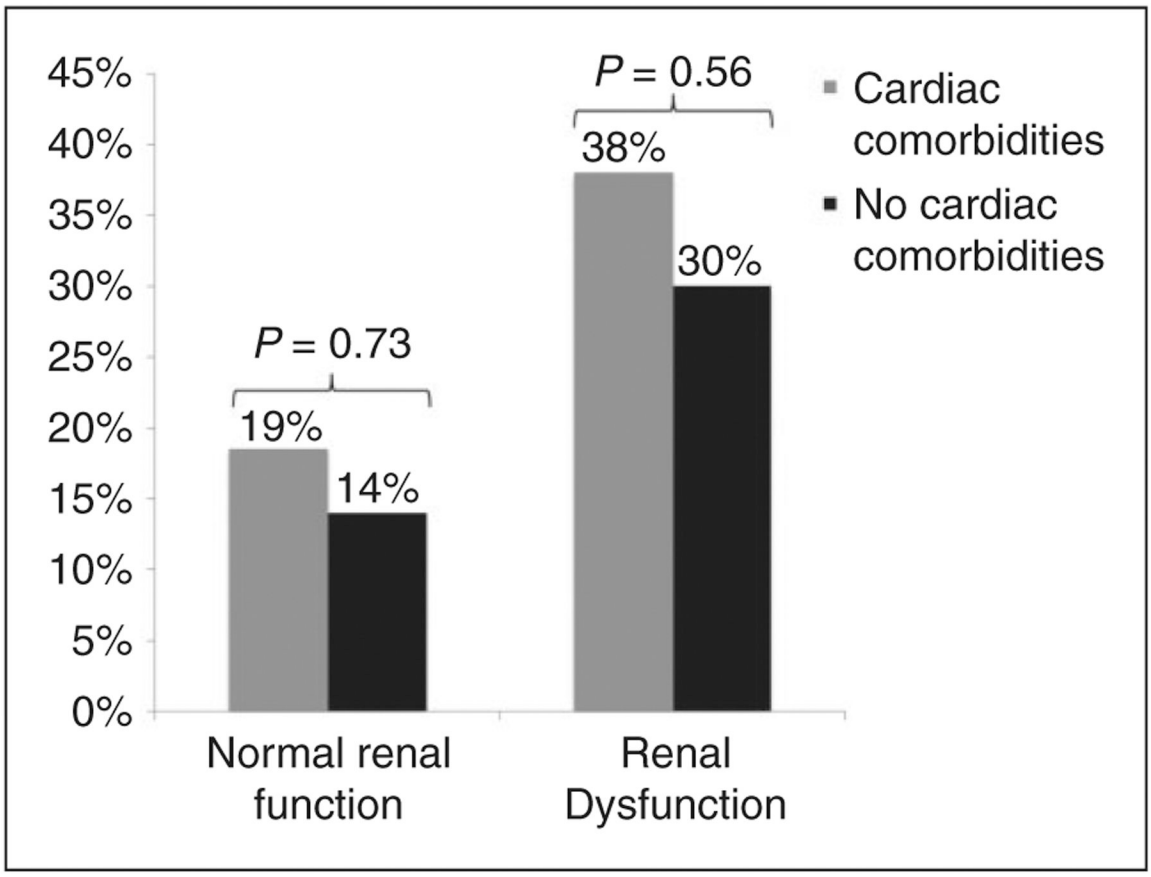

Figure 1.
The percentage of patients that developed grade >3 cardiotoxicity in the presence or absence of baseline cardiac comorbidities in each renal function group.

Table 1.

Decitabine-associated adverse events and literature-reported incidence.[4,7]

	Incidence (%)[a]		Incidence (%)[a]
Cardiovascular		**Central nervous system**	
Peripheral edema	27	Fatigue	46
Hypotension	11	Fever	36
Hypertension	6	Insomnia	14
Tachycardia	8	Intracranial hemorrhage	<5
Heart failure	<5	Confusion	8
Atrial fibrillation	<5	Dizziness	21
Chest pain	6		
Myocardial infarction	<5	**Gastrointestinal**	
		Nausea	40
Endocrine		Constipation	30
Hyperglycemia	6	Diarrhea	28
Hypoalbuminemia	7	Vomiting	16
Hypomagnesemia	5	GI hemorrhage	<5
Hypokalemia	12	Stomatitis/mucositis	11
Hyponatremia	19	Anorexia	23
		GERD	5
Hepatic		Oral pain	5
Hyperbilirubinemia	6	Abdominal pain	14
ALP increase	11		
AST/ALT increase	10	**Infectious**	
		Sepsis	6
Respiratory		Catheter infection	8
Cough	27	Lung infection	20
Dyspnea	29	Febrile neutropenia	20
Pharyngitis	16	Cellulitis	9
Respiratory hemorrhage	<5	URTI	10
Hypoxia	10		

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	Incidence (%)[a]		Incidence (%)[a]
Pulmonary edema	6		
Pleural effusion	5		
Epistaxis	13		

ALP: alkaline phosphatase; AST: aspartate transaminase; ALT: alanine transaminase; URTI: upper respiratory tract infection; GI: gastrointestinal.

[a]Reported incidence for decitabine 20 mg/m^2 daily for five days of a 28-day cycle.

Table 2.

Baseline characteristics.

	Normal renal function (*n* = 63) No. of patients (%)	Renal dysfunction (*n* = 48) No. of patients (%)	*p*-Value
Female	24 (38.1)	26 (54.2)	0.12[c]
De novo disease	39 (62)	31 (64)	0.84[c]
Relapsed disease	15 (24)	8 (17)	0.48[c]
AML arising from MDS	9 (14)	9 (19)	0.61[c]
Previous anthracycline[a]	16 (25)	13 (27)	1.0[c]
Prior AML therapy	13 (21)	9 (19)	1.0[c]
	Median [IQR]	Median [IQR]	
Age	68 [64–72]	73 [68–80]	<0.001[d]
ECOG PS	1 [1–2]	1 [0–2]	0.53[d]
HCT-CI±	1 [1–3]	1 [0–3]	0.53[d]
CrCl (mL/min)	83 [68–100]	46 [40–53]	<0.001[d]
SCr (g/dL)	0.8 [0.7–0.9]	1.1 [0.9–1.6][b]	<0.001[d]

CrCl: creatinine clearance; SCr: serum creatinine; IQR: interquartile range; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MDS: myelodysplastic syndrome

± HCT-CI is a score derived from assessment of comorbidities (e.g. hepatic, pulmonary, cardiovascular, renal, immunologic) that represents risk before allogeneic transplant.[13]

[a]Including treatment for other malignancies.

[b]For patients with a CrCl < 30 mL/min, SCr median [IQR]: 3.8 [2.1–5.1].

[c]Data were analyzed using two-sided Fisher exact tests.

[d]Data were analyzed using two-sided Mann-Wilcoxon-Whitney rank tests.

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Table 3.

Significant toxicities

	Any grade			Grade 3 or greater		
	Normal renal function (*n* = 63)	**Renal dysfunction (*n* = 48)**	***p*-Value[a]**	**Normal renal function (*n* = 63)**	**Renal dysfunction (*n* = 48)**	***p*-Value[a]**
CV	31 (49%)	31 (65%)	0.12	10 (16%)	16 (33%)	0.042
Peripheral edema	17 (27%)	14 (29%)	0.83	-	-	
Hypotension	10 (l6%)	7 (l5%)	1.0	6 (10%)	5 (10%)	1.0
Hypertension	8 (l3%)	13 (27%)	0.085	3 (5%)	6 (l3%)	0.17
Tachycardia	1 (2%)	6 (13%)	0.041	-	1 (2%)	0.43
Heart failure	-	4 (8.3%)	0.033	-	4 (8.3%)	0.033
Atrial fibrillation	6 (l0%)	7 (15%)	0.55	1 (2%)	3 (6%)	0.31
Chest pain	3 (5%)	3 (6%)	1.0	1 (2%)	-	1.0
MI	-	2 (4%)	0.19	-	2 (4%)	0.19
CNS	46 (73%)	43 (90%)	0.033	7 (11%)	7 (15%)	0.77
Fatigue	37 (59%)	35 (73%)	0.16	7 (11%)	5 (10%)	1.0
Fever	7 (11%)	5 (l0%)	1.0	-	-	
Insomnia	7 (11%)	4 (8%)	0.75	-	-	
ICH	1 (2%)	3 (6%)	0.31	-	1 (2%)	0.43
AMS	1 (2%)	1 (2%)	1.0	-	-	
Confusion	5 (8%)	5 (l0%)	0.74	1 (2%)	1 (2%)	1.0
Dizziness	7 (11%)	13 (27%)	0.045	2 (3%)	1 (2%)	1.0
Respiratory	39 (62%)	37 (77%)	0.10	9 (l4%)	19 (40%)	0.0037
Cough	15 (24%)	l4 (29%)	0.29	-	-	
Dyspnea	24 (38%)	24 (50%)	0.25	4 (6%)	6 (13%)	0.32
Pharyngitis	3 (5%)	6 (l3%)	0.17	-	-	
Respiratory hemorrhage	1 (2%)	-	1.0	1 (2%)	-	1.0
Hypoxia	13 (21%)	15 (31%)	0.27	6 (l0%)	11 (23%)	0.065
Pulmonary edema	4 (6%)	4 (8%)	0.73	1 (2%)	4 (8%)	0.16
Pleural effusion	1 (2%)	3 (6%)	0.31	-	1 (2%)	0.43
Epistaxis	7 (11%)	8 (17%)	0.42	-	1 (2%)	0.43
Respiratory Failure	3 (5%)	7 (15%)	0.097	3 (5%)	7 (l5%)	0.097

Note: Data are *n* (%).MI: myocardial infarction; ICH: intracranial hemorrhage; AMS: altered mental status; CNS: central nervous system.

[a] Data were analyzed using two-sided Fisher's exact tests.

Table 4.

Other toxicities

	Any grade			Grade 3 or greater		
	Normal renal function (*n* = 63)	**Renal dysfunction (*n* = 48)**	***p*-Value[a]**	**Normal renal function (*n* = 63)**	**Ater Renal dysfunction (*n* = 48)**	***p*-Value[a]**
Endocrine	48 (76%)	38 (79%)	0.82	1 (l8%)	7 (15%)	0.80
Hyperglycemia	34 (54%)	22 (46%)	0.45	1 (2%)	3 (6%)	0.31
Albumin decrease	40 (64%)	33 (69%)	0.69	7 (11%)	3 (6%)	0.51
Hypomagnesemia	7 (11%)	10 (21%)	0.19	-	-	
Hypokalemia	23 (37%)	l7 (35%)	0.70	2 (3%)	-	0.50
Hyponatremia	27 (43%)	26 (54%)	0.26	2 (3%)	2 (4%)	1.0
Gastrointestinal	49 (78%)	38 (79%)	1.0	6 (l0%)	10 (21%)	0.11
Nausea	24 (38%)	20 (42%)	0.84	1 (2%)	1 (2%)	1.0
Constipation	16 (25%)	18 (38%)	0.21	-	-	
Diarrhea	20 (32%)	20 (42%)	0.32	4 (6%)	7 (15%)	0.20
Vomiting	10 (l6%)	10 (21%)	0.62	1 (2%)	-	1.0
GI hemorrhage	1 (2%)	1 (2%)	1.0	1 (2%)	-	1.0
Mucositis	4 (6%)	8 (17%)	0.12	-	1 (2%)	0.43
Anorexia	23 (37%)	24 (50%)	0.18	1 (2%)	-	1.0
GERD	4 (6%)	2 (4%)	0.70	-	-	
Oral pain	2 (3%)	4 (8%)	0.40	-	-	
Abdominal pain	8 (13%)	10 (21%)	0.30	-	2 (4%)	0.18
Hepatic	34 (54%)	21 (44%)	0.34	5 (8%)	7 (15%)	0.36
Bilirubin increase	15 (24%)	10 (21%)	0.82	2 (3%)	3 (8%)	0.65
ALP increase	10 (l6%)	5 (10%)	0.58	1 (2%)	-	1.0
AST/ALT increase	27 (43%)	l7 (35%)	0.44	3 (5%)	3 (6%)	1.0
Infectious	34 (54%)	29 (60%)	0.56	33 (52%)	28 (58%)	0.57
Sepsis	11 (l8%)	9 (19%)	1.0	11 (17%)	9 (19%)	1.0
Catheter infection	7 (11%)	7 (15%)	0.77	7 (11%)	7 (15%)	0.77
Lung infection	9 (14%)	14 (29%)	0.063	9 (14%)	14 (29%)	0.063
URTI	4 (6%)	2 (4%)	0.70	1 (2%)	-	1.0
FN	27 (43%)	23 (48%)	0.70	27 (43%)	23 (48%)	0.70

	Any grade			Grade 3 or greater		
	Normal renal function (*n* = 63)	**Renal dysfunction (*n* = 48)**	***p*-Value[a]**	**Normal renal function (*n* = 63)**	**Ater Renal dysfunction (*n* = 48)**	***p*-Value[a]**
Cellulitis	2 (3%)	2 (4%)	1.0	2 (3%)	2 (4%)	1.0
Other infections	3 (5%)	6 (13%)	0.17	1 (2%)	3 (6%)	0.31

Note: Data are *n* (%). GI: gastrointestinal; GERD: gastroesophageal reflux disease; ALP: alkaline phosphatase; AST: aspartate transaminase; ALT: alanine transaminase; URTI: upper respiratory tract infection; FN: febrile neutropenia.

[a]Data were analyzed using two-sided Fisher's exact tests.

Table 5.

Secondary end points.

	Normal renal function (*n* = 63)	**Renal dysfunction (*n* = 48)**	
	No. of patients (%)	**No. of patients (%)**	***p*-Value**
30-Day all-cause mortality	4 (6.3%)[a]	10 (20.8%)[b]	0.041[c]
Hospitalization during cycle I	31 (49.2%)	27 (56.3%)	0.57[c]
Cycle 2 dose delay	11 (17.5%)	4 (8.3%)	0.26[c]
Treatment discontinuation after cycle I	6 (9.5%)	8 (16.7%)	0.38[c]
	Median [IQR]	Median [IQR]	
Hospital length of stay (days)	7 [4–12]	8 [4–12]	0.41[d]

IQR: interquartile range.

[a]Three patients died of sepsis and one of leukemia.

[b]Two patients died of sepsis, five of respiratory failure, and three of leukemia.

[c]Data were analyzed using two-sided Fisher's exact tests.

[d]Data were analyzed using two-sided Mann–Wilcoxon–Whitney rank tests.