Hematological Oncology
Hematol Oncol 2015; **33**: 67–74
Published online 8 April 2014 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2141

Original Research Article

A double-blind, randomized, controlled trial on *N*-acetylcysteine for the prevention of acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation

Sara Ataei[1], Molouk Hadjibabaie[1,2], Amirhossein Moslehi[1], Maryam Taghizadeh-Ghehi[2]*, Asieh Ashouri[2], Elham Amini[3], Kheirollah Gholami[1,2], Alireza Hayatshahi[4], Mohammad Vaezi[5] and Ardeshir Ghavamzadeh[5]

[1]*Clinical Pharmacy Department, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*
[2]*Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran*
[3]*Department of Pharmaceutical Care, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[4]*Department of Pharmacy Practice, School of Pharmacy, Loma Linda University, Loma Linda, CA, USA*
[5]*Hematology–Oncology and Stem Cell Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran*

**Correspondence to: Maryam Taghizadeh-Ghehi, Pharm.D., Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, 4th floor, No. 92, Karimkhan Zand Ave, Hafte Tir Sq., Tehran, Iran. E-mail: taghizadehgm@razi.tums.ac.ir*

Received 3 March 2014
Accepted 5 March 2014

Abstract

Acute kidney injury (AKI) is one of the complications of hematopoietic stem cell transplantation and is associated with increased mortality. *N*-acetylcysteine (NAC) is a thiol compound with antioxidant and vasodilatory properties that has been investigated for the prevention of AKI in several clinical settings. In the present study, we evaluated the effects of intravenous NAC on the prevention of AKI in allogeneic hematopoietic stem cell transplantation patients. A double-blind randomized placebo-controlled trial was conducted, and 80 patients were recruited to receive 100 mg/kg/day NAC or placebo as intermittent intravenous infusion from day −6 to day +15. AKI was determined on the basis of the Risk–Injury–Failure–Loss–End-stage renal disease and AKI Network criteria as the primary outcome. We assessed urine neutrophil gelatinase-associated lipocalin (uNGAL) on days −6, −3, +3, +9 and +15 as the secondary outcome. Moreover, transplant-related outcomes and NAC adverse reactions were evaluated during the study period. Statistical analysis was performed using appropriate parametric and non-parametric methods including Kaplan–Meier for AKI and generalized estimating equation for uNGAL. At the end of the trial, data from 72 patients were analysed (NAC: 33 patients and placebo: 39 patients). Participants of each group were not different considering baseline characteristics. AKI was observed in 18% of NAC recipients and 15% of placebo group patients, and the occurrence pattern was not significantly different ($p = 0.73$). Moreover, no significant difference was observed between groups for uNGAL measures ($p = 0.10$). Transplant-related outcomes were similar for both groups, and all patients had successful engraftment. Three patients did not tolerate NAC because of abdominal pain, shortness of breath and rash with pruritus and were dropped from the intervention group before transplantation. However, the frequency of adverse reactions was not significantly different between groups. In conclusion, our findings could not show any clinical benefits from high-dose NAC particularly for AKI prevention in allogeneic hematopoietic stem cell transplantation patients. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: **acute kidney injury; *N*-acetylcysteine; hematopoietic stem cell transplantation; urine neutrophil gelatinase-associated lipocalin; randomized controlled trial**

Introduction

Hematopoietic stem cell transplantation (HSCT) is used increasingly to treat several malignant and non-malignant hematological disorders as well as solid tumours [1]. Numerous complications and treatment-related toxicities including renal impairment may limit the outcomes of HSCT [2]. Renal impairment can also be associated with other HSCT complications including sinusoidal occlusion syndrome, acute graft-versus-host disease (GvHD), sepsis and thrombotic microangiopathies [3,4].

Acute kidney injury (AKI) is a prevalent complication in HSCT patients and usually occurs within the first month after transplant [1]. However, the incidence, timing and

severity of AKI vary between myeloablative and non-myeloablative HSCT. The prevalence of AKI is reported to be 21–73% for myeloablative allogeneic HSCT, and the conditioning regimen has been shown to be an independent risk factor for AKI development [5]. Several factors have been associated with AKI in myeloablative HSCT including sinusoidal occlusion syndrome, female sex, co-morbidity, hypertension, acute GvHD and the use of amphotericin B [6–8]. Moreover, cyclosporine has also been shown to be a major cause of AKI in allogeneic HSCT [9–11].

Acute kidney injury is associated with increased short-term and long-term mortality, and studies have shown two to three times higher mortality rate in HSCT patients with AKI [6,12]. In addition, literature has revealed that prevention of AKI might reduce the severity of non-renal organ dysfunction, incidence and severity of chronic kidney disease and mortality rate [3,4,13]. Therefore, preserving renal function is crucial for HSCT patients.

Antioxidant agents including *N*-acetylcysteine (NAC) have been evaluated for the prevention and treatment of different HSCT complications [14–17]. NAC is a thiol compound with antioxidant and vasodilatory properties that has also been investigated for the prevention of contrast-induced nephropathy [18,19]. Among several meta-analysis studies, one reported significant effects of NAC for the prevention of contrast-induced nephropathy [20]; however, other publications including a more recent one have revealed heterogeneity and conflicting results [21–23]. Some preclinical and scant human studies on drugs other than contrast media agents have reported positive effects of NAC for nephrotoxicity prophylaxis [19,24,25]. Although the mechanisms of NAC nephroprotection are unclear, literature shows that the decrease of vasoconstriction and oxygen-free radical generation might play a role in the prevention of contrast-induced nephropathy [26].

Considering the AKI aetiologies in HSCT patients and the aforementioned findings, NAC could be beneficial for the prevention of AKI. To the extent of our knowledge, no previous studies have evaluated such nephroprotective effects of NAC in this setting. Therefore, the aim of the present study was to investigate the effects of NAC on the prevention of AKI in HSCT patients during hospitalization.

Materials and methods

Study design

This study was a double-blind, randomized, placebo-controlled trial that was conducted at the Hematology–Oncology and Stem Cell Transplant Research Center, Tehran University of Medical Sciences (Iran), between October 2012 and September 2013. The protocol was reviewed and approved by the Ethics Committee of the institution. An informed written consent was obtained from each patient prior to the study (trial registration ID: IRCT201306031030N14).

Study population and hematopoietic stem cell transplantation procedure

We recruited acute myelogenous leukaemia, acute lymphoblastic leukaemia and myelodysplastic syndrome patients aged 15–60 years old who were admitted to receive allogeneic HSCT. Exclusion criteria were patients with hypertension, chronic kidney disease and diabetes mellitus.

The myeloablative conditioning regimen started 6 days before transplantation (day −6) and included 4 mg/kg oral busulfan in divided daily doses for 4 days (total dose 16 mg/kg) followed by 60 mg/kg intravenous cyclophosphamide, once daily for 2 days (total dose 120 mg/kg). Patients received peripheral blood hematopoietic stem cells 1 day after completion of chemotherapy.

Prophylaxis regimens against GvHD consisted of cyclosporine (1.5 mg/kg intravenously daily from day −3 then 3 mg/kg from day +7) with a short course of methotrexate (10 mg/m^2 on day +1 and 6 mg/m^2 on days +3, +6 and +11). Cyclosporine trough levels were monitored weekly or if the dosing was modified. Infection prophylaxis and treatment as well as supportive care were administered according to the institutional protocols. Acute GvHD was graded according to the Glucksberg *et al*. criteria [27].

Study groups

We randomly allocated patients to NAC or placebo group using a blocked randomization schedule. Patients in the intervention group received 100 mg/kg/day NAC (Exir Pharmaceuticals Company, Borujerd, Iran, 2 g/ampule) from days −5 to +15. NAC daily dose was diluted in 500 mL 5% dextrose water and administered as an intermittent intravenous infusion over 3 h. The placebo (Exir Pharmaceuticals Company, Borujerd, Iran, ampule) was administered in the same schedule as the NAC. Physicians, nursing staff, patients and data collectors were all blind to study group allocations. One investigator assessed inclusion and exclusion criteria, allocated patients to the study groups and provided the NAC or placebo to the nursing staff.

Study outcomes and data collection

The primary study outcome was AKI occurrence that was defined on the basis of the Risk–Injury–Failure–Loss–End-stage renal disease (RIFLE) and AKI Network (AKIN) criteria. The severity of kidney injury in patients

DOI: 10.1002/hon

who developed AKI was determined according to both aforementioned criteria [28,29]. Serum creatinine was measured daily using the Jaffe method and documented from the admission day until day +15.

Urine neutrophil gelatinase-associated lipocalin (uNGAL) concentration was assessed as a secondary outcome. In order to measure uNGAL, urine samples were collected at baseline (day −6) and days −3, +3, +9 and +15. Samples were stored at −70°C, and an assay was performed using the human neutrophil gelatinase-associated lipocalin enzyme-linked immunosorbent assay kit (cat. no. RD191102200R, BioVendor-Laboratorní medicína a.s., Brno, Czech Republic).

Transplant-related outcomes including timing of neutrophil and platelet engraftment, fever occurrence and acute GvHD frequency and severity were also evaluated during hospital stay.

Patients' characteristics including age, gender, weight, height, underlying disease and complete remission status were recorded at baseline. The glomerular filtration rate at baseline was estimated using the Cockcroft–Gault equation [30]. Dosing and administration duration of nephrotoxic drugs were also documented during study period.

Statistical analysis

A sample size of 80 patients (with statistical power of 80% and a type 1 error of 0.05) was calculated on the basis of the reported AKI rate of 50% in non-total body irradiation myeloablative allogeneic HSCT patients while assuming a reduction of the AKI rate to 30% as clinical efficacy [1,21,31].

We used median (range), mean (SD) or frequency (percentage) to describe the study population. According to the Kolmogorov–Smirnov test of normality, independent-sample *t*-test or Mann–Whitney *U* test was performed to compare continuous variables. A chi-square test was used to compare categorical data. Kappa statistic was calculated to assess the agreement of AKIN and RIFLE definitions for AKI detection. The primary outcome (AKI occurrence) was compared between study groups using Kaplan–Meier estimation and log rank test. Cox proportional hazard regression was performed to investigate the association of several covariates with the AKI occurrence.

We performed a generalized estimating equation (GEE) model to compare uNGAL measures between two treatment groups as we had repeated measures on individual subjects and to account for the missing data. In the GEE model, we entered uNGAL as the dependent variable and the study groups and baseline uNGAL as the independent variables. The working correlation matrix was defined as autoregressive in the model. We considered a p-value <0.05 to be significant in all statistical tests.

Results

Of 80 recruited patients, data were collected and analysed from 72 participants. In the NAC group, three patients discontinued the drug before transplantation because of abdominal pain, shortness of breath and rash with pruritus. Four patients in the NAC and one patient in the placebo group were dropped out because of lack of cooperation with collecting urine samples, that is, no urine samples were taken. The flow diagram of study participants is illustrated in Figure 1. No significant difference was observed between groups considering gender, age, disease, complete remission status and baseline estimated glomerular filtration rate. The patients' demographic and clinical characteristics are summarized in Table 1.

Acute kidney injury occurrence was not significantly different between NAC and placebo groups on the basis of both AKIN and RIFLE criteria ($p=0.74$ and 0.97, respectively). We observed a high agreement between AKIN and RIFLE criteria (kappa values = 0.948, $p<0.001$), and the following results are presented according to the AKIN criteria. Table 2 presents a summary of AKI occurrence and severity in the study groups.

We found no relationship between AKI occurrence and patients' gender ($p=0.31$), age ($p=0.20$), disease ($p=0.26$) and complete remission status ($p=0.93$). However, use of amphotericin B deoxycholate before AKI onset was related to a higher rate of AKI in all study patients ($p=0.01$). Association of vancomycin use with AKI occurrence was not significant ($p=0.07$). To investigate the association of cyclosporine trough levels with AKI occurrence, patients were categorized according to the trough levels (two analysis approaches: >200 or >300 μg/L at least one time). No significant associations were found between cyclosporine trough levels and AKI ($p=0.43$ and 0.82).

A summary of uNGAL concentrations and ratios is provided in Table 3. The uNGAL concentrations on different days were not significantly different between study groups (p-values >0.05). Further analysis on the uNGAL concentration ratios (day +3, +9 or +15 to baseline) also revealed no significant difference between groups (p-values >0.05). There was no significant effect of intervention on uNGAL concentrations when controlling for the time of measurement (days −3, +3, +9 and +15) and the baseline concentration ($p=0.10$).

Transplant-related outcomes were not significantly different between two groups (Table 4). Although a higher rate of severe acute GvHD (grades 3 and 4) was observed in the placebo group (20%) than in the NAC (6%) group, the difference was not statistically significant ($p=0.08$). In addition, no association was found between acute GvHD and AKI occurrence ($p=0.18$).

Regarding the administration of nephrotoxic drugs, we did not observe any significant differences between NAC and placebo groups for amphotericin B deoxycholate

DOI: 10.1002/hon

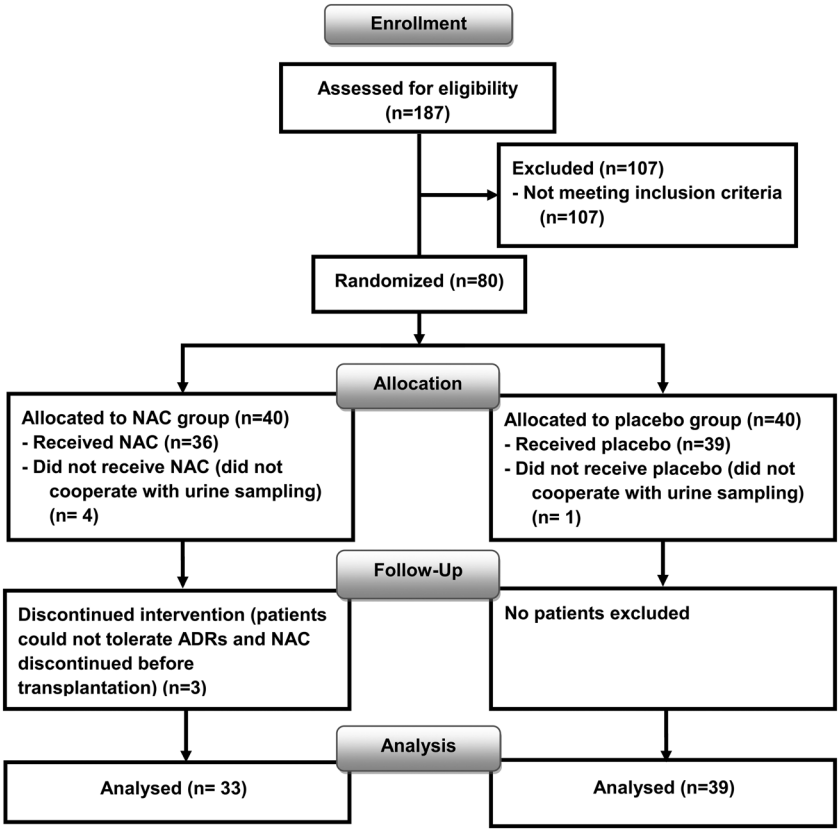

Figure 1. Flow diagram of study participants

Table 1. Patients demographic and clinical characteristics

	NAC ($n=33$)	Placebo ($n=39$)	*p*-value
Age (year), mean (*SD*)	35.0 (11)	30 (10)	0.06
BMI (kg/m^2), mean (*SD*)	24.4 (4)	25.1 (4.4)	0.52
Female sex, no. (%)	11.0 (33)	10 (26)	0.47
Diagnosis, no. (%)			0.80[a]
AML	16.0 (48.5)	18 (46)	
ALL	16.0 (48.5)	17 (44)	
MDS	1.0 (3)	4 (10)	
CR status, no. (%)			0.75[b]
CR1	27.0 (82)	33 (85)	
CR2	6.0 (18)	5 (13)	
CR3	0.0 (0)	1 (3)	
eGFR (ml/min), mean (*SD*)	114.0 (29)	125 (37)	0.19

[a]*p*-value reported for comparison of patients with AML and ALL.
[b]*p*-value reported for comparison of patients in CR1 and others.
AML, acute myelogenous leukaemia; ALL, acute lymphoblastic leukaemia; BMI, body mass index; CR, complete remission; eGFR, estimated glomerular filtration rate; MDS, myelodysplastic syndrome; NAC, *N*-acetylcysteine; SD, standard deviation.

Table 2. Occurrence of acute kidney injury in study patients

	NAC ($n=33$)	Placebo ($n=39$)	*p*-value
AKI occurrence, no. (%)			
RIFLE criteria	5 (15)	6 (15)	0.97
AKIN criteria	6 (18)	6 (15)	0.73
AKI stages, no. (%)			
Risk/injury (RIFLE criteria)	3/2	2/4	—[a]
I/II (AKIN criteria)	4/2	2/4	—[a]

[a]Subgroup analysis was not performed because of small number of patients who developed AKI.
AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; NAC, *N*-acetylcysteine; RIFLE, Risk–Injury–Failure–Loss–End-stage renal disease.

(21% vs 23%, $p=0.85$), vancomycin (51% vs 61%, $p=0.73$) and amikacin (3% vs 5%, $p=0.65$). All patients received cyclosporine for GvHD prophylaxis, and the frequency of patients in the aforementioned trough-level categories was similar between NAC and placebo groups (>200 μg/L: 39% vs 54%, $p=0.08$; >300 μg/L: 24% vs 31%, $p=0.36$).

Frequency of patients' complaints during NAC administration was not different between two groups (Table 5). NAC was discontinued in 5 of 33 patients in the NAC group before day +15, owing to drug intolerance with patients' complaints of nausea/vomiting, abdominal pain, shortness of breath and cough. No severe adverse effects such as anaphylactoid reactions occurred.

DOI: 10.1002/hon

Table 3. Summary of urine NGAL measures

Factors	NAC ($n = 33$)		Placebo ($n = 39$)		*p*-value
	No.	Median (min, max)	No.	Median (min, max)	
Urine NGAL (ng/ml)					0.10[a]
Baseline (day −6)	30	1.20 (0.10, 14)	34	1.20 (0.20, 41)	0.72
Day −3	31	1.20 (0.20, 34)	35	0.50 (0.20, 12)	0.46
Day +3	29	2.10 (0.10, 19)	31	1.20 (0.20, 10)	0.32
Day +9	27	2.10 (0.10, 63)	34	2.25 (0.10, 21)	0.88
Day +15	23	6.10 (0.10, 20)	32	3.15 (0.20, 28)	0.65
Day +3/day −6 ratio	26	1.31 (0.03, 12)	28	0.88 (0.01, 15)	0.09
Day +9/day −6 ratio	24	1.04 (0.20, 25)	30	0.90 (0.01, 55)	0.65
Day +15/day −6 ratio	21	3.40 (0.02, 100)	29	1.50 (0.01, 43)	0.34

[a]*p*-value reported on the basis of the generalized estimating equation method for comparison of urine NGAL concentration on mentioned days between groups.
NAC, *N*-acetylcysteine; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4. Transplant-related outcomes

	NAC ($n = 33$)	Placebo ($n = 39$)	*p*-value
Platelet engraftment time[a]	11 (8, 14)	10 (7, 18)	0.91
Neutrophil engraftment time[b]	12 (8, 17)	12 (9, 17)	0.14
Fever, no. (%)	29 (88)	36 (92)	0.40
Acute GvHD occurrence, no. (%)	3 (8)	16 (41)	0.22
Acute GvHD grades, no. (%)			0.13
I	3 (9)	3 (8)	
II	4 (12)	5 (13)	
III	1 (3)	3 (8)	
IV	1 (3)	5 (13)	

[a]Median (min, max) of days after transplantation when patients had platelet count ≥20 000 cells/mm^3 lasting three consecutive days without transfusions.
[b]Median (min, max) of the first day of three consecutive days with an absolute neutrophil count of ≥500 cells/mm^3 after transplantation.
GvHD, graft-versus-host disease; NAC, *N*-acetylcysteine.

Table 5. Frequency of NAC adverse reactions

		NAC[a] ($n = 36$), no. (%)	Placebo ($n = 39$), no. (%)	*p*-value
Gastrointestinal	Abdominal pain	18 (50.0)	28 (71.8)	0.05
	Nausea and vomiting	25 (69.4)	32 (82.1)	0.20
Respiratory	Shortness of breath	5 (13.9)	3 (7.7)	0.31
	Cough	9 (25.0)	16 (41.0)	0.14
Dermatologic	Rash with pruritus	1 (2.8)	0 (0.0)	0.48

NAC, *N*-acetylcysteine.
[a]Frequency of NAC adverse reactions is reported in all patients who received NAC, including three patients who could not tolerate the drug and were dropped out from the study.

Discussion

N-acetylcysteine has been investigated for the prevention of contrast-induced nephropathy in different clinical settings [18,22]. In addition, NAC has been evaluated as a prophylactic agent for non-contrast-induced kidney injury, mostly in preclinical studies [19]. In the present study, we evaluated the efficacy of NAC as an AKI prophylaxis in the HSCT setting. Furthermore, we assessed uNGAL as a sensitive biomarker of kidney damage [32,33]. Our findings did not show any significant differences in AKI occurrence between study groups. AKI seemed to be

DOI: 10.1002/hon

more severe in the control group; however, subgroup analysis could not be performed because of the low frequency of AKI. Our study results did not show any significant differences in uNGAL concentrations between NAC and placebo groups.

Acute kidney injury frequency (18% in NAC and 15% in the placebo group) in our patients was lower than previously reported rates after myeloablative allogeneic HSCT (21–73%) [1,4]. In a recent study at our centre, AKI rate (defined as a twofold increase in serum creatinine from baseline) was reported to be 42% in allogeneic HSCT patients who received non-total body irradiation-based myeloablative conditioning regimen [31]. In another study at our centre, AKI was defined on the basis of the AKIN criteria and reported to occur in 45.7% of HSCT patients [34]. Ando *et al*. reported an AKI rate of 66% and 61% on the basis of RIFLE and AKIN criteria in myeloablative HSCT [35]. However, any comparison of such studies should be carried out cautiously because of different myeloablative conditioning regimens, variations in AKI definition, diversity in patients' diseases, donor human leucocyte antigen matching and the stem cell source [3,4,7,36].

It should be noted that the reported median time to onset of AKI in the aforementioned studies varies from 7 to 40 days, and it usually occurs within the first 2–4 weeks post-transplant in allogeneic myeloablative HSCT [4]. Hence, the relatively short follow-up duration (up to day +15) might have underestimated the AKI rate in the present study.

Moreover, our study patients were mostly young male adults, in their first complete remission state, with no underlying organ dysfunction and receiving peripheral blood stem cells from human leucocyte antigen-matched related donor following non-total body irradiation myeloablative conditioning regimen. These characteristics could have resulted in a lower AKI rate in our study patients. Although some of these characteristics were proposed to be risk factors for AKI [1], we could not find any association between AKI occurrence and baseline characteristics in our study. It is in line with studies that could not confirm age, gender and underlying disease as risk factors for AKI [1,6].

The study groups were similar with regard to factors affecting kidney function. Patients' age, gender, underlying diseases and complete remission status were not significantly different between groups. The rate of acute GvHD, as a risk factor for AKI [1], was also similar in the study groups. We should mention that the rate of severe acute GvHD (grades 3 and 4) was higher in the placebo group in comparison with the NAC group (20% vs 6%). On the contrary, a previous trial on the effect of NAC for liver toxicity management in HSCT patients revealed that the risk of moderate acute GvHD was higher in NAC recipients [16,37]. Future studies with adequate power and follow-up periods are suggested to evaluate the impact of NAC on the GvHD rate.

All patients received cyclosporine as GvHD prophylaxis, and the frequency of a high trough level was not different in the two study groups. Evidence on the association of cyclosporine nephrotoxicity with the drug blood levels is controversial [4,38], and we could not find any association between cyclosporine trough levels and AKI occurrence in the present study. Other potentially nephrotoxic medications including amphotericin B deoxycholate, vancomycin and aminoglycosides were administered to some of our study patients either alone or in combination; however, the frequency of use was not different between NAC and placebo groups. In line with studies demonstrating nephrotoxic drugs to be risk factors for AKI [1,4], our results showed that amphotericin B deoxycholate use was associated with AKI in all study patients.

N-acetylcysteine adverse drug reactions were similar between our study groups; however, few patients could not tolerate NAC adverse reactions, and the drug was discontinued because of abdominal pain, shortness of breath and rash with pruritus. Neither serious adverse drug reactions nor infusion-related side effects such as anaphylactoid reactions occurred in the NAC group. This finding is in agreement with another study on high-dose intravenous NAC in HSCT patients [16]. Nevertheless, larger studies with adequate sample size are required to investigate the safety profile of high dose intravenous NAC.

The route of NAC administration might be an important factor in clinical efficacy as several mechanism have been proposed for the nephroprotective effects including antioxidant, vasodilatory and direct protective activities [19]. Considering NAC antioxidant properties via glutathione repletion, some studies have shown that orally administered NAC may produce higher glutathione levels in comparison with bioequivalent intravenous doses [39]. However, some animal studies have failed to show a significant correlation between nephroprotective effects and glutathione levels [21]. Regarding the direct protective effects and favourable pharmacokinetic profile of intravenous NAC, it has been postulated as the optimal administration route for AKI prevention in contrast-induced nephropathy, but the results are inconsistent [21].

According to the aforementioned roles of intravenous NAC in AKI prevention, the required daily dose of NAC and patients' oral intolerance, we decided to employ the intravenous route.

Limitations

In the present study, we observed a lower AKI frequency in comparison with similar studies that might have affected the study power. Frequent missed urine samples and a relatively short follow-up were major limitations of the current study. Although the uNGAL biomarker is highly sensitive to kidney injury, it might be influenced by

DOI: 10.1002/hon

extrarenal sources, systemic infection and inflammatory conditions [40]. However, the fever rate was not different between two groups in our study. In addition, as the renal function is highly variable in HSCT patients, a more frequent assessment of the uNGAL biomarker might have been required to detect kidney injury.

In conclusion, the present study did not show any benefit from high-dose NAC for AKI prevention in allogeneic HSCT patients. However, these results should be interpreted with caution considering our study limitations, particularly the short-term follow-up.

Future studies should also investigate the potential of the uNGAL biomarker to predict AKI in the HSCT setting.

Conflict of interest

The authors have no competing interest.

Acknowledgment

We would like to thank the staff of BMT wards, particularly Ms Mousavi, Ms Shahriari and Ms Khalilvand, for their contribution in conducting the trial. This study was supported by a grant from the research council of Hematology–Oncology and Stem Cell Transplant Research Center, Tehran University of Medical Sciences (grant number: 92-02-36-22907) and was carried out as a dissertation project for clinical pharmacy residency.

References

1. Lopes JA, Jorge S. Acute kidney injury following HCT: incidence, risk factors and outcome. *Bone Marrow Transplant* 2011; **46**(11): 1399–1408.
2. Yang W-C, Chen Y-T, Chang W-W, *et al.* Outcome predictors of allogeneic hematopoietic stem cell transplant. *Am J Med Sci* 2013; **345**(1): 33–38.
3. Parikh CR, Coca SG. Acute renal failure in hematopoietic cell transplantation. *Kidney Int* 2006; **69**(3): 430–435.
4. Kogon A, Hingorani S. Acute kidney injury in hematopoietic cell transplantation. *Semin Nephrol* 2010; **30**(6): 615–626.
5. Parikh CR, Schrier RW, Storer B, *et al.* Comparison of ARF after myeloablative and nonmyeloablative hematopoietic cell transplantation. *Am J Kidney Dis* 2005; **45**(3): 502–509.
6. Kersting S, Koomans HA, Hene RJ, Verdonck LF. Acute renal failure after allogeneic myeloablative stem cell transplantation: retrospective analysis of incidence, risk factors and survival. *Bone Marrow Transplant* 2007; **39**(6): 359–365.
7. Hingorani SR, Guthrie K, Batchelder A, *et al.* Acute renal failure after myeloablative hematopoietic cell transplant: incidence and risk factors. *Kidney Int* 2005; **67**(1): 272–277.
8. Parikh CR, McSweeney PA, Korular D, *et al.* Renal dysfunction in allogeneic hematopoietic cell transplantation. *Kidney Int* 2002; **62**(2): 566–573.
9. Parikh CR, Sandmaier BM, Storb RF, *et al.* Acute renal failure after nonmyeloablative hematopoietic cell transplantation. *J Am Soc Nephrol* 2004; **15**(7): 1868–1876.
10. Lopes JA, Goncalves S, Jorge S, *et al.* Contemporary analysis of the influence of acute kidney injury after reduced intensity conditioning haematopoietic cell transplantation on long-term survival. *Bone Marrow Transplant* 2008; **42**(9): 619–626.
11. Liu H, Li YF, Liu BC, *et al.* A multicenter, retrospective study of acute kidney injury in adult patients with nonmyeloablative hematopoietic SCT. *Bone Marrow Transplant* 2010; **45**(1): 153–158.
12. Lopes JA, Jorge S, Goncalves S, *et al.* Contemporary analysis of the influence of acute kidney injury (AKI) after myeloablative hematopoietic cell transplantation on long-term patient's survival. *Bone Marrow Transplant* 2008; **42**(2): 139–141.
13. Parikh CR, McSweeney P, Schrier RW. Acute renal failure independently predicts mortality after myeloablative allogeneic hematopoietic cell transplant. *Kidney Int* 2005; **67**(5): 1999–2005.
14. Mansouri A, Hadjibabaie M, Iravani M, *et al.* The effect of zinc sulfate in the prevention of high-dose chemotherapy-induced mucositis: a double-blind, randomized, placebo-controlled study. *Hematol Oncol* 2012; **30**(1): 22–26.
15. Jahangard-Rafsanjani Z, Gholami K, Hadjibabaie M, *et al.* The efficacy of selenium in prevention of oral mucositis in patients undergoing hematopoietic SCT: a randomized clinical trial. *Bone Marrow Transplant* 2013; **48**(6): 832–836.
16. Barkholt L, Remberger M, Hassan Z, *et al.* A prospective randomized study using *N*-acetyl-L-cysteine for early liver toxicity after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008; **41**(9): 785–790.
17. Thornley I, Lehmann LE, Sung L, *et al.* A multiagent strategy to decrease regimen-related toxicity in children undergoing allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2004; **10**(9): 635–644.
18. Fishbane S. *N*-acetylcysteine in the prevention of contrast-induced nephropathy. *Clin J Am Soc Nephrol* 2008; **3**(1): 281–287.
19. Rushworth GF, Megson IL. Existing and potential therapeutic uses for *N*-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. *Pharmacol Ther* 2014; **141**(2): 150–159.
20. Trivedi H, Daram S, Szabo A, Bartorelli AL, Marenzi G. High-dose *N*-acetylcysteine for the prevention of contrast-induced nephropathy. *Am J Med* 2009; **122**(9): 874.e9–874.e15.
21. Sun Z, Fu Q, Cao L, Jin W, Cheng L, Li Z. Intravenous *N*-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. *PLoS One* 2013; **8**(1): e55124.
22. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of *N*-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; **65**(4): 1366–1374.
23. Kshirsagar AV, Poole C, Mottl A, *et al.* N-acetylcysteine for the prevention of radio contrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; **15**(3): 761–769.
24. Hosseinjani H, Moghaddas A, Khalili H. N-acetylcysteine for the prevention of non-contrast media agent-induced kidney injury: from preclinical data to clinical evidence. *Eur J Clin Pharmacol* 2013; **69**(7): 1375–1390.
25. Ocak S, Gorur S, Hakverdi S, Celik S, Erdogan S. Protective effects of caffeic acid phenethyl ester, vitamin C, vitamin E and N-acetylcysteine on vancomycin-induced nephrotoxicity in rats. *Basic Clin Pharmacol Toxicol* 2007; **100**(5): 328–333.
26. Radomska-Leśniewska DM, Skopiński P. N-acetylcysteine as an anti-oxidant and anti-inflammatory drug and its some clinical applications. *Centr Eur J Immunol* 2012; **37**(1): 58–66.
27. Glucksberg H, Storb R, Fefer A, *et al.* Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974; **18**(4): 295–304.
28. Mehta RL, Kellum JA, Shah SV, *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**(2): R31.

DOI: 10.1002/hon

29. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**(4): R204–R212.
30. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**(1): 31–41.
31. Saddadi F, Najafi I, Hakemi MS, Falaknazi K, Attari F, Bahar B. Frequency, risk factors, and outcome of acute kidney injury following bone marrow transplantation at Dr Shariati Hospital in Tehran. *Iran J Kidney Dis* 2010; **4**(1): 20–26.
32. Carrillo-Esper R, Castillo-Albarran FM, Perez-Jauregui J. Neutrophil gelatinase-associated lipocalin: a novel biomarker in acute kidney injury. *Cir Cir* 2011; **79**(6): 577–581.
33. Haase M, Bellomo R, Haase-Fielitz A. Neutrophil gelatinase-associated lipocalin. *Curr Opin Crit Care* 2010; **16**(6): 526–532.
34. Ghehi MT, Rezaee S, Hayatshahi A, *et al.* Vancomycin pharmacokinetic parameters in patients undergoing hematopoietic stem cell transplantation (HSCT). *Int J Hematol Oncol Stem Cell Res* 2013; **7**(4): 1–9.
35. Ando M, Mori J, Ohashi K, *et al.* A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT. *Bone Marrow Transplant* 2010; **45**(9): 1427–1434.
36. Helal I, Byzun A, Rerolle JP, Morelon E, Kreis H, Bruneel-Mamzer MF. Acute renal failure following allogeneic hematopoietic cell transplantation: incidence, outcome and risk factors. *Saudi J Kidney Dis Transpl* 2011; **22**(3): 437–443.
37. Karlsson H, Nava S, Remberger M, Hassan Z, Hassan M, Ringden O. N-acetyl-L-cysteine increases acute graft-versus-host disease and promotes T-cell-mediated immunity in vitro. *Eur J Immunol* 2011; **41**(4): 1143–1153.
38. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol* 2009; **4**(2): 481–508.
39. Shalansky S, Pate G, Levin A, Webb J. N-acetylcysteine for prevention of radiocontrast induced nephrotoxicity: the importance of dose and route of administration. *Heart* 2005; **91**(8): 997–999.
40. Wasilewska A, Zoch-Zwierz W, Taranta-Janusz K, Michaluk-Skutnik J. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of cyclosporine nephrotoxicity? *Pediatr Nephrol* 2010; **25**(5): 889–897.

DOI: 10.1002/hon