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Original Article

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Predictors of Acute Kidney Injury in Hematological Cancer Patients: A Prospective Cross-Sectional Study

Maryam Ghasemi[1], Mohammad Solduzian[2], Marzieh Shahrabi[1], Hamidreza Taghvaye-Masoumi[3], Molouk HadjiBabaei[1,4], Hosein Kamran Zadeh[5], Kourosh Sadeghi[1]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Pharm D, Tabriz, Iran
[3]Department of Clinical Pharmacy, Faculty of Pharmacy, Guilan University of Medical Science, Guilan, Iran
[4]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran
[5]Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Objective: Data about the contribution of drugs to the development of acute kidney injury are scarce in hematological cancer patients. The current study evaluated the relationship between the use of different medications and acute kidney injury development in hematological cancer patients.

Methods: This study was designed as a prospective observational cross-sectional study. All patients admitted to hematology wards of Shariati Hospital of Tehran University of Medical Sciences were evaluated, and patients younger than 18 years of age, those who were not able to consent to participate and those who presented with acute kidney injury were excluded. Acute kidney injury was diagnosed per KDIGO criteria.

Results: Overall, 450 patients were evaluated in this study and 138 cases of acute kidney injury were detected; this translates into 30.6% incidence rate in hematology wards of the study center. The median age of the patients with acute kidney injury was 49 years and 84 (60.9%) of them were men. Length of hospital stay and mortality rate was significantly higher in patients with acute kidney injury than those without ($P < .001$ and $< .001$, respectively). Results of the multivariate analysis showed that treatment with vancomycin (odds ratio 1.77), the combination of vancomycin and amphotericin B deoxycholate (odds ratio 3.10), and idarubicin (odds ratio 2.10) could significantly increase the odds of acute kidney injury development in patients with hematological malignancy, but treatment with hydrocortisone (odds ratio 0.26) could have significant nephroprotective effects.

Conclusion: This study showed that treatment with vancomycin, the combination of vancomycin and amphotericin B deoxycholate, and idarubicin could significantly increase the odds of acute kidney injury development. Hydrocortisone treatment showed significant nephroprotective effects. Mortality and duration of hospital stay were significantly higher in patients with acute kidney injury.

Keywords: Acute kidney injury, hematologic malignancies, risk factors

Corresponding author: Kourosh Sadeghi ✉ Kourosh.Sadeghi@gmail.com

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INTRODUCTION

Acute kidney injury (AKI) is a pathologic process that results in toxic metabolite accumulation and complications of the disease course.[1] AKI development is evaluated by the changes observed in serum creatinine (SrCr) and urine output in a specific timeline and routine practice kidney disease: Improving Global Outcomes (KDIGO) criteria is used for its diagnosis and staging.[2]

The prevalence of AKI in newly diagnosed hematological cancer patients has been reported to be about 70%, however, lower rates have been reported in some types such as acute promyelocytic leukemia.[3,4] Different factors might contribute to the development of AKI in hematological cancer patients, and its etiology is multifactorial.[5] Sepsis and hypo perfusion have been reported as the main etiologic causes of AKI in hematological cancer patients.[6] Chemotherapy is recognized as

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the most significant risk factor for AKI development in patients with hematological cancers.[7]

The chance of AKI development increases with increasing age, and higher rates are reported in those older than 65 years; also other factors such as neutropenia, nephrotoxic medication receipt, tumor lysis syndrome, electrolyte, and coagulation abnormalities are known as risk factors for AKI development.[8]

Development of AKI could complicate the hospitalization course and result in undesired dose adjustment of important medications. It has been reported that AKI could lower survival and remission rates in patients with hematological cancers.[3] AKI could result in a significant increase in mortality rates and hospital length of stay.[9] Higher rates of mortality have been reported in patients with hematological cancers requiring dialysis because of AKI.[10] Increased mortality rates in patients with AKI and cancer have been shown to be unrelated to baseline cancer type.[5]

Drug dosing in patients with AKI could pose a challenge to clinicians and require therapeutic drug monitoring and dose adjustment per medication level, in order to optimize efficacy and prevent adverse events.[11] Inconvenient dosing of medication could lower their effectiveness and result in higher treatment failure, different drug pharmacokinetics, and pharmacodynamics factors could be altered in patients with AKI, and this will make it challenging to achieve a proper drug serum level and correlate these levels with therapeutic effects.[12] Using recommendations for drug dose adjustment in patients with chronic kidney disease (CKD) might not be reasonable as it has been shown that this could result in low and inappropriate serum levels and increase the possibility of treatment failure.[13]

Although the role of chemotherapeutic agents in the development of AKI in hematological cancer patients is well known, data about the contribution of other drugs to the development of this problem are scarce.[7] Considering that AKI could have such drastic effects on survival and complicate the hospitalization course, the current study was designed to evaluate the relationship between receipt of different medications and intravenous fluids with AKI development in hematological cancer patients and to identify actual and adjustable risk factors to minimize their effects.

MAIN POINTS

- Vancomycin or vancomycin in combination with amphotericin B deoxycholate could cause acute kidney injury (AKI) in hematological cancer patients.
- Anthracyclines could induce AKI in patients with hematological cancer.
- Hydrocortisone could have nephroprotective effects in patients with hematological cancer.
- AKI increases mortality and hospitalization in patients with hematological cancer.

METHODS

This study was designed as a prospective observational and cross-sectional study to identify risk factors and the rate of AKI development. All patients admitted between April 2019 and February 2020 to hematology wards of Shariati hospital of Tehran University of Medical Sciences were evaluated for enrollment in the study.

The protocol of the study was reviewed and approved by the ethical committee of the Tehran University of Medical Sciences and the approval code of IR.TUMS.TIPS.REC.1398.006 was given on April 17, 2019.

All patients older than 18 years of age who were admitted to the hematology wards A, B, and C of Shariati hospital were enrolled in the study and were asked to sign an informed consent note first.

Patients younger than 18 years of age and those who were not able to consent to participate in the study were excluded; also, patients who presented with AKI as the first sign of hematological cancer were excluded from the study. KDIGO criteria were used for diagnosis of AKI.[2]

Demographic data, including the patient's age, weight, gender, and past medical history, were recorded. Baseline hematological data, chemotherapeutic agents used, and other drugs were collected for each patient. Length of hospital stay, hematological laboratory data, Blood urea nitrogen (BUN), Srcr, and serum electrolytes were also recorded.

Statistical Analysis

All of the possible risk factors for AKI development were totally and solely evaluated for their contribution to the occurrence of the event. Backward data selection was used for data enrollment in the final multivariate analysis, and data with a *P*-value of less than .05 in univariate analysis was evaluated in the final multivariate analysis. The logistic regression model was used to evaluate the significance of each factor's part in AKI occurrence. Odds ratio (OR) and *P*-value for each factor were reported. The continuous data with normal distribution are reported as mean ± SD and those without normal distribution as median with interquartile range (IQR).

RESULTS

Overall, 450 patients were evaluated in this study, and 138 cases of AKI were detected; this translated into 30.6% incidence rate of AKI in the hematology wards of the study center. Demographic data, baseline diagnosis, maintenance fluids, mortality rate, and length of hospital stay of evaluated patients can be seen in Table 1. Acute kidney injury was more prevalent in patients with baseline kidney disease ($P < .001$). Baseline diagnosis

Table 1. Demographic Data, Baseline Diagnosis, and Maintenance Fluid Contribution to AKI Development and Comparison Between Two Groups (AKI and non-AKI) In Terms of Mortality and Duration of Hospitalization

Variable	Patients Without AKI	Patients With AKI	*P-value*
Number of patients	312	138	N/A
Age (years), median (IQR)	45.5 (32-60)	49 (33-62)	.18
Gender, N (%)			.53
Male	180 (57.7%)	84 (60.9%)	
Female	132 (42.3%)	54 (39.1%)	
Weight (kg), Mean ± SD	72.48 ± 11.31	70.31 ± 13.60	.12
Height (cm), Mean ±SD	169.74 ± 18.96	168.04 ± 21.91	.46
Past medical history, N (%)			
Hypertension	82 (26.3%)	28 (20.3%)	.17
Diabetes mellitus	27 (8.7%)	11 (7.9%)	.79
Kidney disease	0 (0%)	9 (6.5%)	**<.001**
Liver disease	2 (0.6%)	1 (0.7%)	.92
Diagnosis, N (%)			**.02**
Acute myelogenous leukemia	102 (32.7%)	72 (52.2%)	
Acute lymphoblastic leukemia	45 (14.4%)	13 (9.4%)	
Chronic myelogenous leukemia	8 (2.6%)	2 (1.5%)	
Chronic lymphoblastic leukemia	10 (3.2%)	0 (0%)	
Multiple myeloma	13 (4.2%)	9 (6.5%)	
Hodgkin lymphoma	5 (1.6%)	1 (0.7%)	
Non-Hodgkin lymphoma	9 (2.9%)	1 (0.7%)	
Hairy cell leukemia	1 (0.3%)	0 (0%)	
Aplastic anemia	23 (7.4%)	6 (4.3%)	
Final hematologic disease was not available at the time	96 (30.8%)	34 (24.6%)	
Maintenance intravenous fluids N (%)			**<.001**
Normal saline	85 (27.2%)	56 (40.6%)	
Half normal saline	9 (2.9%)	3 (2.2%)	
Dextrose 3.33%/NaCl 0.3% (combination fluid)	9 (2.9%)	11 (8%)	
Uric acid (mg/dl), median (IQR)	4 (3.1-5.4)	5.1 (4.25-6.65)	**<.001**
Duration of hospitalization (days), median (IQR)	11.5 (7-26)	25 (13-41)	**<.001**
Mortality, N (%)	68 (21.8%)	71 (51.8%)	**<.001**

AKI, acute kidney injury; IQR, interquartile range.

Table 2. Univariate Analysis of Relevance of Medication Administration and AKI Development

Presence of Risk Factor	Patients Without AKI, N (%)	Patients With AKI, N (%)	*P*-value
Vancomycin	167 (53.5%)	108 (78.3%)	**<.001**
Meropenem	223 (71.5%)	111 (80.4%)	.05
Liposomal amphotericin B	0 (0%)	9 (6.5%)	**<.001**
Amphotericin B deoxycholate	58 (18.6%)	69 (50%)	**<.001**
Caspofungin	23 (7.4%)	20 (14.6%)	**.02**
Acyclovir (prophylactic dose)	165 (52.9%)	88 (63.8%)	**.03**
Voriconazole	67 (21.5%)	40 (29%)	.08
Methotrexate (high dose)	36 (11.5%)	7 (5.1%)	.04
Imipenem	18 (5.8%)	4 (2.9%)	.2
Amikacin	11 (3.5%)	9 (6.5%)	.16
Cyclosporine	23 (7.4%)	16 (11.6%)	.5
Vancomycin + amphotericin B deoxycholate	54 (17.3%)	59 (42.7%)	**<.001**
Vancomycin + aminoglycoside	11 (3.5%)	8 (5.8%)	.27
Vancomycin + cyclosporine	4 (1.3%)	5 (3.6%)	.11
Conventional doxorubicin	14 (4.5%)	7 (5.1%)	.78
Arsenic trioxide	11 (3.5%)	7 (5.1%)	.44
Bortezomib	5 (1.6%)	2 (1.5%)	.90
Cyclophosphamide	17 (5.5%)	9 (6.5%)	.65
Cytarabine	89 (28.6%)	50 (36.2%)	.11
Daunorubicin	15 (4.8%)	7 (5.1%)	.90
Dexamethasone	120 (38.6%)	51 (37%)	.74
Etoposide	8 (2.6%)	3 (2.2%)	.80
Filgrastim	66 (21.1%)	43 (31.2%)	.02
Fludarabine	9 (2.9%)	6 (4.3%)	.43
Hydrocortisone	176 (56.4%)	49 (35.5%)	**<.001**
Hydroxyurea	58 (18.6%)	38 (27.6%)	**.03**
Idarubicin	31 (10%)	35 (25.4%)	**<.001**
Imatinib	8 (2.6%)	5 (3.6%)	.53
Mercaptopurine	3 (1%)	4 (2.9%)	.14
Methylprednisolone	33 (10.6%)	5 (3.6%)	**.02**
Mitoxantrone	10 (3.2%)	7 (5.1%)	.34
Rituximab	18 (5.7%)	4 (2.9%)	.2
Tretinoin	7 (2.2%)	7 (5.1%)	.12
Vincristine	38 (12.2%)	12 (8.7%)	.27

The numbers might not add up because of missing data.
AKI, acute kidney injury.

was significantly different between two groups (P = .015), and higher number of patients with AKI were diagnosed with AML [72 (52.2%) vs. 102 (32.7%)]. Uric acid levels were significantly higher in patients with AKI (P < .001). Also, patients with AKI spent longer time in hospital (P < .001). Mortality rate was also significantly higher in patients with AKI compared to those without [71 (51.8%) vs. 68 (21.8%), P < .001]. Medication administration data of the evaluated patients could be seen in Table 2. Vancomycin (P < .001), meropenem (P = .046), amphotericin B deoxycholate and liposomal amphotericin B (P < .001 and <.001, respectively), combination of vancomycin and amphotericin B deoxycholate (P < .001), caspofungin (P = .02), prophylactic acyclovir (with a dose of 400 mg orally twice daily) (P = .032), high-dose methotrexate (MTX) (defined as doses ≥ 500 mg/m^2) (P = .036), filgrastim (P = .023), hydroxyurea (P = .034), idarubicin (P < .001), hydrocortisone, and methylprednisolone (P < .001 and .02, respectively) were significantly related to AKI development in univariate analysis.

Medication administration data of patients with stage 3 AKI is shown in Table 3. More patients in the AKI group received normal saline [11 (45.9%) vs. 45 (39.8%)], and this was significantly associated with stage 3 AKI development in univariate analysis (P = .037). Also, the combination of vancomycin and amphotericin B deoxycholate (P = .017) was significantly associated with stage 3 AKI development in univariate analysis.

Baseline and post-AKI major electrolyte and hematological laboratory data are shown in Table 4. Only serum sodium, creatinine, and BUN were significantly different (P = .01, <.001, and <.001, respectively). Other variables did not show significant change compared to baseline.

The results of the multivariate analysis of different risk factors' contribution to AKI development are reported in Table 5. Of the medications which patients received, idarubicin (OR: 2.1, P = .029), vancomycin (OR: 1.77, P = .041), and combination of vancomycin and amphotericin B deoxycholate (OR: 3.10, P < .001) significantly increased the odds of AKI development. Treatment with hydrocortisone was significantly related to decreased risk of AKI development (OR = 0.26, P < .001).

The results of multivariate analysis regarding different risk factors contributing to stage 3 AKI development are shown in Table 6. The combination of vancomycin and amphotericin B deoxycholate significantly raised the odds of stage 3 AKI development (P = .04, OR = 1.55, 95% CI: 1.05-2.47).

DISCUSSION

The current study evaluated the contribution of different factors to the development of AKI in hematological cancer patients. The results indicate that AKI was associated with higher mortality and more extended hospital stay and complicated the hospitalization course. The rate of AKI development was 30.6% in the current study which was lower compared to the reported rates

Table 3. Univariate Analysis of Relevance of Medication Administration and Stage 3 AKI Development

Presence of Risk Factor		Patients Without Stage 3 AKI, N (%)	Patients With Stage 3 AKI, N (%)	*P*-value
Vancomycin		91 (80.5%)	17 (70.8%)	.29
Meropenem		92 (81.4%)	19 (79.2%)	.79
Liposomal amphotericin B		8 (7.1%)	1 (4.2%)	.60
Amphotericin B deoxycholate		62 (54.9%)	8 (33.3%)	.05
Caspufungin		15 (13.4%)	4 (16.7%)	.67
Acyclovir (prophylactic)		74 (65.5%)	14 (58.3%)	.50
Voriconazole		33 (29.2%)	8 (33.3%)	.68
Methotrexate (high dose)		4 (3.5%)	3 (12.5%)	.07
Imipenem		3 (2.6%)	2 (8.3%)	.20
Amikacin		8 (7.1%)	2 (8.3%)	.83
Cyclosporine		12 (10.6%)	2 (8.3%)	.95
Vancomycin + amphotericin B deoxycholate		55 (48.7%)	5 (20.8%)	**.02**
Vancomycin + aminoglycoside		7 (6.2%)	2 (8.3%)	.70
Vancomycin + cyclosporine		4 (3.5%)	1 (4.2%)	.88
Conventional doxorubicin		5 (4.4%)	2 (8.3%)	.78
Arsenic trioxide		7 (6.2%)	0 (0%)	.21
Bortezomib		2 (1.8%)	0 (0%)	.99
Cyclophosphamide		7 (6.2%)	2 (8.3%)	.70
Cytarabine		41 (36.3%)	8 (33.3%)	.78
Doxorubicin		5 (4.4%)	2 (8.3%)	.43
Dexamethasone		40 (35.4%)	12 (50%)	.18
Etoposide		2 (1.8%)	1 (4.2%)	.48
Filgrastim		35 (31%)	9 (37.5%)	.53
Fludarabine		5 (4.4%)	1 (4.2%)	.95
Hydrocortisone		40 (35.4%)	9 (37.5%)	.84
Hydroxyurea		31 (27.4%)	7 (29.2%)	.86
Idarubicin		31 (27.4%)	4 (6.7%)	.27
Imatinib		4 (3.5%)	1 (4.2%)	.88
Mercaptopurine		4 (3.5%)	0 (0.00%)	.99
Methylprednisolone		5 (4.4%)	1 (4.2%)	.95
Mitoxantrone		5 (4.4%)	2 (8.3%)	.43
Rituximab		2 (1.8%)	2 (8.3%)	.11
Vincristine		10 (8.8%)	2 (8.3%)	.93
Maintenance intravenous fluids	Normal saline	45 (39.8%)	11 (45.9%)	**.04**
	Half normal saline	3 (2.6%)	0 (0.0%)	
	Dextrose 3.33% /NaCl 0.3% (combination fluid)	6 (5.3%)	5 (20.8%)	

AKI, acute kidney injury.

Table 4. Baseline and Post-AKI Electrolyte and Hematological Laboratory Data

Test Results	Baseline	Following AKI	*P-value*
WBC (number/ml), median (IQR)	2030 (390-9860)	3050 (590-11 450)	.26
Hemoglobin (g/dl), Mean ± SD	7.16 ± 3.14	7.86 ± 1.68	.13
Platelets (number/ml), median (IQR)	23 000 (7000-61 000)	26 000 (12 000-66 000)	.07
Serum creatinine (mg/dl), median (IQR)	0.99 (0.85-1.24)	1.81 (1.55-2.29)	**<.001**
Blood urea nitrogen (mg/dl), median (IQR)	20 (13-29)	33.85 (24-48)	**<.001**
Calcium level (mg/dl), median (IQR)	8 (7.4-8.8)	7.8 (7-8.4)	.36
Phosphor level (mg/dl), median (IQR)	4.1 (2.9-5.2)	3.8 (2.9-5.2)	.78
Sodium level (meq/L), median (IQR)	140 (136-142.5)	140 (137-144)	**.01**
Potassium level (meq/L), median (IQR)	3.81 (3.4-4.37)	3.9 (3.28-4.47)	.36
Magnesium level (mg/dl), median (IQR)	2 (1.8-2.3)	2.1 (1.7-2.5)	.44

AKI, acute kidney injury; IQR, interquartile range; WBC, white blood cell; SD, standard deviation.

in some of the previous studies but close to some others.[3,4,7] Present study provides reliable data regarding the role of medications in the development of hematological cancer patients and adds data to previous findings.

We showed that baseline kidney disease is associated with higher rates of AKI. This finding correlates with the previous findings of good quality which count CKD as a risk factor for AKI.[14]

Table 5. Multivariate Analysis of Relevance of Medication Administration and AKI Development

Presence of Risk Factor (Drugs)	*P-value*	Odds Ratio	CI
Idarubicin	**.03**	2.10	1.07-4.11
Vancomycin	**.04**	1.77	1.02-3.07
Vancomycin + Amphotericin B deoxycholate	**<.001**	3.10	1.76-5.47
Filgrastim	.07	1.68	0.96-2.94
Hydrocortisone	**<.001**	0.26	0.15-0.45
Hydroxyurea	.51	1.21	0.68-2.16
Caspofungin	.40	1.41	0.63-3.16
Acyclovir	.86	1.04	0.63-1.71

AKI, acute kidney injury; CI, confidence interval.

Table 6. Multivariate Analysis of Relevance of Medication Administration and Stage 3 Acute Kidney Injury Development

Presence of Risk Factor (drugs)	*P-value*	Odds Ratio	Confidence interval
Vancomycin + amphotericin B deoxycholate	**.04**	1.55	1.05-2.47
Maintenance intravenous fluids	.06	0.32	0.11-0.95

Acute kidney injury

has been shown to be related to higher mortality rates in patients with malignancy. The results of our study endorse the previous findings, as it is shown that mortality rate was higher in patients experiencing AKI.[15] Also, our results indicate that AKI was associated with longer hospital stays. Extended hospital stay indicates the complication of the hospitalization course. It is contemplated as an expected outcome of the AKI, since it has been reported that AKI increases hospital stay duration and extra charges of patient management.[16]

Uric acid levels were significantly higher in patients who experienced AKI. The relation between high uric acid levels and AKI development has been shown in previous well-designed studies, and the findings of our study are in correlation with those reports.[17]

Baseline diagnosis of evaluated patients was significantly different between the two groups. Higher proportion of patients with AKI was diagnosed with AML. The rate of AKI has been reported to be high in patients with AML.[3] Interestingly, of the routine medication used in induction therapy of patients with AML, idarubicin was significantly associated with the development of AKI as it was shown by the multivariate analysis. It is possible that AML itself could also contribute to AKI development, but confirmation of this issue needs further study.

Both volume depletion and overload have been shown to increase the rates of AKI. Results of the univariate analysis of the current study showed that hypotonic fluids could significantly increase the odds of AKI development, this is in correlation with the findings of previous studies, which concluded that balanced solutions are associated with improved kidney outcomes.[18] This finding was not confirmed by the multivariate analysis, it could have been because of the supposed dehydration as the cause of AKI by physicians and the expectation that saline administration could help reverse the process which apparently has not been the case. Therefore, further investigation is required to evaluate this issue. Herein one could assume that multiple factors could have masked the effects of maintenance fluids.

Amphotericin B is a known nephrotoxic medication, and reports of about 60% AKI occurrence are available with its use and receiving co-medications such as furosemide or

angiotensin-converting enzyme inhibitors has been shown to increase the possibility of this adverse effect.[19] Retrospective evaluation of patients, who received lower than recommended doses of liposomal amphotericin B, reported strikingly lower rates of AKI with this medication compared to those previously reported with amphotericin B deoxycholate.[20] Even some available information from randomized controlled trials approves of this point.[21] Results of the univariate analysis in our study showed that both conventional and liposomal amphotericin B could raise the odds of AKI development in hematological malignancy patients, but multivariate analysis failed to confirm these findings. The doses utilized in patients enrolled in our study were based on the recommendations of the current National Comprehensive Cancer Network and patients received the high dose of 5 mg/kg/day of liposomal amphotericin B and 1.5 mg/kg/day of conventional amphotericin B, which are higher compared to doses evaluated in previous studies.[22] Almost all the patients enrolled in the current study were started on amphotericin B deoxycholate, because of its lower cost and shortage of liposomal amphotericin B, and later in the hospitalization course were switched to liposomal form in case of infusion reaction or certain diagnosis. The overall number of patients who received liposomal amphotericin B was limited (6.5% of patients who developed AKI). These issues make a clear conclusion about the nephrotoxic effects of different formulations of amphotericin B in AKI development.

Retrospective reviews have reported AKI occurrence rate of about 16% in patients with hematological malignancies who received vancomycin.[23] Concomitant treatment with nephrotoxic medications in combination with administration of higher doses of vancomycin to provide adequate antibacterial effects against some methicillin-resistant staphylococci could result in higher rates of AKI.[24] Vancomycin trough levels higher than 15 mg/liter have been reported to significantly increase the odds of AKI development.[25] Median vancomycin level of patients evaluated in our study was 19.24 (IQR: 12.89-23.44). Increased odds of AKI development with vancomycin were seen in the current study as well, and it is in correlation with the findings of the previous studies in patients with hematological malignancies. Multivariate analysis showed that the combination of vancomycin and amphotericin B deoxycholate was significantly associated with AKI development, however, multivariate analysis failed to prove the association between treatment with either form of amphotericin and AKI development. It has been reported that amphotericin B could significantly increase the risk of AKI in patients treated with vancomycin and our findings also supported this finding.[26,27] Our study also showed that a combination of vancomycin and amphotericin B deoxycholate could significantly increase the odds of stage 3 AKI development, indicating that this combination might pose a serious threat to the kidney of patients and should be used carefully and under strict monitoring where absolutely required.

Multivariate analysis of data gathered in the study showed that treatment with certain anthracyclines could significantly be related to AKI development. Drug information databases might underreport this adverse effect in patients treated with these medications, while there are actual data that reported AKI following treatment with anthracyclines. In a study, 160 urine and serum samples from 66 pediatric cancer patients were evaluated and idarubicin-induced AKI was reported, although it should be mentioned that the main monitoring parameter was *N*-acetyl-β-D-glucosaminidase activity indices and creatinine levels did not show a significant rise.[28] Data with doxorubicin are less robust, but its nephrotoxic effects have been demonstrated in animal studies.[29] Results of our study indicated that idarubicin could be significantly related to AKI development in patients with hematological malignancies, as demonstrated by the results of multivariate analysis. Further prospective studies are required to clearly define the rates of this adverse effect and its clinical significance.

Treatment with MTX could have nephrotoxic effects and this adverse effect occurs in a dose-related manner. The rates of nephrotoxicity with low-dose MTX have been reported to be about 2%, while previous studies in hematological malignancy patients reported that following treatment with high-dose MTX, nephrotoxicity of any grade might occur in up to about 39% of patients.[30,31] Univariate analysis of our investigation supported the reported nephrotoxic effects of high-dose MTX, but the multivariate analysis did not show significant effects. Acute kidney injury occurred in 5.1% of the patients who received this medication. Hydration and urine alkalinization were ordered and carefully monitored in all patients who received high-dose MTX in our center. This could have resulted in lower rates of AKI with this agent in our study.

Previous reports have shown that hydrocortisone could have nephroprotective effects and might lower mortality rates in patients with AKI.[32] Although nephroprotective effects of low-dose hydrocortisone have mainly been reported in patients with sepsis, our data indicate that this medication could have similar effects in patients with hematological malignancies. The beneficial effects of hydrocortisone might be the results of its action in conserving the endothelial glycocalyx, improved tissue perfusion, which could be severely impaired in hematological cancer patients, or decreased inflammation that is known to be related to AKI.[33-35]

Limitations

There are some limitations to our study. First, the dose adjustment after AKI development and the outcome of this action could have been evaluated. Second outcomes other than death or need for dialysis could also be evaluated. Unfortunately, urine output is not routinely monitored in our center and this has complicated the process of AKI diagnosis in our patients, although laboratory criteria were strictly followed.

CONCLUSION

Longer hospitalization courses and higher mortality rates in patients with AKI and hematological malignancy were observed in our study. Also, the results of this study showed that treatment with vancomycin, a combination of vancomycin and amphotericin B deoxycholate, and idarubicin could significantly contribute to the development of AKI in patients with hematological malignancies. Frequent monitoring and limitation of nephrotoxic drug use could be helpful in patients receiving these medications. Treatment with hydrocortisone showed nephroprotective effects.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Tehran (Approval no: IR.TUMS.TIPS.REC.1398.006, Date: April 17, 2019).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Supplementary Table 1. KDIGO criteria for diagnosis and staging of Acute Kidney Injury (AKI)		
	Serum creatinine concentration criteria	**Urine output criteria**
Definition	Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days	Or Urine output of <0.5 mL/kg/hour for >6 hours
Stage 1	Increase in serum creatinine of ≥0.3 mg/dL or 1.5 to 1.9 times baseline	Or Urine output of <0.5 mL/kg/hour for 6 to 12 hours
Stage 2	Increase in serum creatinine to 2.0 to 2.9 times baseline	Or Urine output of <0.5 mL/kg/hour for 12 to 24 hours
Stage 3	Increase in serum creatinine to ≥3.0 times baseline Or Increase in serum creatinine of ≥0.3 mg/dL to ≥4.0 mg/dL	Or Urine output of <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours Or Initiation of renal replacement therapy