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Urinary Specific Gravity (USG) as an Assessment Tool for the Management of Dehydration in Head and Neck Cancer Patients Receiving Chemo-Radiation with Weekly Cisplatin

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Abstract

Background: Concomitant chemo-radiation therapy (CRT) with cisplatin is the mainstay of treatment for patients with locally advanced head and neck cancer. Nephrotoxicity is a well-documented adverse effect of cisplatin, which is exacerbated by dehydration, a common complication in this group of patients. This study prospectively assessed the utility of urine specific gravity (USG) as a guide for fluid replacement, and its preventive effect in cisplatin induced nephrotoxicity.

Methods: Patients with head and neck cancer who received CRT with weekly cisplatin at our institution were included in the analysis. All patients received 1 L normal saline (NS) with 1 g of magnesium and 10 mEq of potassium pre and post cisplatin. USG was measured weekly, patients with USG>1.020 was considered dehydrated and received 2 L NS twice weekly. Those patients with USG>1.025 while on the twice-weekly regimen were deemed very dehydrated and received 2 L NS daily. The primary objective was renal toxicity of any grade.

Results: 44 patients were identified and completed CRT in less than 7.5 weeks. Eighteen of 44 patients (41%) had initial USG>1.020 and were started on NS twice weekly. By week 5, 44 of 44 patients (100%) needed supplemental fluid hydration with only 4 of 44 (9%) requiring daily IV fluids (IVF). No patient experienced renal toxicity of any grade. Five patients (11%) had grade I hypomagnesemia.

Conclusion: USG is a very sensitive marker of dehydration and can be used as a guide for fluid replacement which can minimize cisplatin induced nephrotoxicity in this population.

Keywords: Urine specific gravity; Dehydration; Cisplatin; Nephrotoxicity; Head and neck cancer; Chemo-radiation therapy

Introduction

Cisplatin-based chemo-radiation therapy (CRT) has been shown to improve survival compared to radiation therapy alone in patients with head and neck cancer [1,2]. Nausea, vomiting and mucositis are common side effects associated with cisplatin-based CRT. Nephrotoxicity is a serious and dose limiting toxicity by cisplatin itself. Cisplatin nephrotoxicity is the composite result of the transport of cisplatin into renal epithelial cells which damages nuclear and mitochondrial DNA, leading to cell death and initiation of a robust inflammatory response [3]. The vomiting and mucositis can lead to clinically significant dehydration which can further put these patients at an increased risk for nephrotoxicity [4]. The impaired renal function resulting from this toxicity can lead to pronounced electrolyte imbalances, notably hypokalemia, hypomagnesemia and acute kidney injury evidenced by elevated blood urea nitrogen (BUN) and creatinine [5]. Due to different scoring systems reported in the literature, the incidence of nephrotoxicity of any grade ranges from 5% to 100% [5].

Identification of hydration status is difficult based on physical exam alone. Many findings associated with dehydration such as skin turgor and dry mucus membranes are subjective and not easily quantified. Plasma osmolality (Posm) is often considered the most validated technique for assessing hydration status. However, because Posm is tested in a laboratory under controlled conditions where body fluids are stable and equilibrated this would be difficult to perform in a typical clinical practice. In practical settings, urinary measurements (i.e., urine osmolality [Uosm] and urine specific gravity [USG]) are cost effective and can be used as to accurately represent hydration status [6].

Currently, there are no established protocols in place for systematic monitoring of fluid status to identify early signs of dehydration.

Developing such a system may help prevent nephrotoxicity through early identification and aggressive intravenous fluid (IVF) administration of patients who are becoming dehydrated before manifesting clear signs and symptoms of dehydration. Here, we report our algorithm using USG, a sensitive method for assessing dehydration that we implemented at our institution for the prevention of cisplatin-induced nephrotoxicity in head and neck cancer patients receiving concomitant CRT with weekly cisplatin.

Materials and Methods

Patients

Between 12/1/2013 and 12/1/2015, patients with a diagnosis of squamous cell carcinoma of the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx or paranasal sinuses, and treated with CRT with weekly cisplatin were included in this analysis. All patients had ECOG performance status of 0-1 and underwent placement of percutaneous endoscopic gastrostomy tube (PEG-tube) before the beginning of CRT for nutritional support [7]. Patients aged 71 years or older had to be independent on instrumental activities of daily living (IADLs), activities of daily living (ADLs), have no falls over the last six months, and have no signs of cognitive impairment assessed by the three-word recall test [8,9]. Patients were required to have adequate baseline renal and hepatic function.

Chemo-radiation therapy

Cisplatin was dose adjusted by age. Patients 71 years and older were treated with 30 mg/m^2 weekly and those 70 and younger with 40 mg/m^2 weekly. All patients received pre- and post-cisplatin hydration intravenously consisting of 1 L of normal saline (NS) with 1g magnesium (Mg) and 10 mEq KCl. Intensity modulated radiation therapy (IMRT) was used for radiation therapy. For definitive radiation therapy (RT), a total dose of 70 Gy was administered; for adjuvant RT, a total dose of 66 Gy was administered; and for neoadjuvant RT, a total dose of 56 Gy was administered. All patients were treated with 2 Gy per fraction and five fractions per week.

Measurement of USG and fluid replacement

All patients provided a urine sample on arrival to the infusion center. This was not required to be the first morning void. Urine specific gravity was measured on a weekly basis using the Clinitek Atlas Urine Chemistry Analyzer, which uses the refractive index method to determine USG. Patients were assigned intervention groups based on results. Patients with USG>1.020 were considered dehydrated and received 2 L NS twice weekly. Those patients who had USG>1.025 while on the twice-weekly regimen were deemed very dehydrated and received 2 L NS daily. Patients were followed with weekly measurement of USG after the end of CRT until obtaining a level of <1.020 without any parenteral fluid supplementation.

Objectives

The primary objective was to assess renal toxicity of any grade. Secondary objectives included assessment of hypokalemia, hypomagnesemia, hyponatremia, hematologic toxicity, mucositis of any grade, disease free survival, cisplatin dose reductions, treatment delays and hospitalizations.

Statistical analysis

Statistical analysis was calculated for the measurements including count/percent for categorical measures and median/range or mean/standard deviation for continuous measures. Paired t-tests were used to compare changes in electrolyte measures. Pre-treatment lab values were taken prior to initiation of CRT. Post-treatment lab values were taken week after CRT was completed. Survival curves for disease free survival (DFS) and overall survival (OS) were plotted using Kaplan-Meier methods. Using these curves, one and two year DFS rates and OS rates were estimated. Toxicities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Results

A total of 44 patients were identified and their characteristics are summarized in Table 1. The median age at diagnosis was 61 years (range 27-77) and the mean age was 60.9 years. Seven patients (16%) were diagnosed with stage III disease, 30 patients (68%) with stage IVa, and 7 patients (16%) with stage IVb. All 44 patients received concomitant CRT with cisplatin. 27 patients (61%) received definitive RT to a total dose of 70 Gy, 14 patients (32%) received adjuvant RT (post-op) to a total radiation dose of 66 Gy, and 3 patients (7%) received neoadjuvant (pre-op) RT to a total dose of 56 Gy. All patients receiving definitive or post-op CRT completed radiation in less than 7.5 weeks. Those receiving pre-op CRT completed radiation in 5.5 weeks.

	Total
No. of patients	44 (100%)
Sex (M/F)	35/9 (79.5%/20.5%)
Median Age (range)	61 (27-77)
Site:	
Oral cavity	5 (11%)
Oropharynx	20 (45%)
Hypopharynx	4 (9%)
Larynx	10 (23%)
Nasopharynx	2 (5%)
Paranasal sinus	3 (7%)
Stage:	
III	7 (16%)
IVa	30 (68%)
IVb	7 (16%)
Treatment:	
Pre-op CRT	3 (7%)
Post-op CRT	14 (32%)
Definitive CRT	27 (61%)

Table 1: Patients' characteristics.

The cisplatin dose intensity according to treatment regimen was as follows: 260 mg/7 weeks (Range 240-280) in definitive or post-op patients ≤ 70 years, 240 mg/6 weeks in pre-op patients; 210 mg/7 weeks in patients >70 years. The reasons for cisplatin dose reduction were grade II neutropenia in 5 patients (11%) and grade II thrombocytopenia in 5 patients (11%). No dose adjustments were made for renal toxicity.

All of the patients in this study experienced severe mucositis. Six of 44 patients (13.5%) experienced grade III mucositis and 38 of 44 patients (86.5%) experienced grade IV mucositis. The average weight loss was 7.5% with a range between 1% and 20%.

Regarding the hydration status, 18/44 patients (41%) were deemed to be dehydrated before the beginning of treatment due to the fact that the USG value was higher than 1.020. All these patients started NS twice a week on week 1. IVF administration is summarized in Table 2. By week 5, 44/44 patients (100%) were on additional IVF. 4/44 patients (9%) had daily IVF due to severe dehydration (USG>1.025).

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 20
Patients	18/44	22/44	40/44	41/44	44/44	44/44	41/44	41/44	10/44	3/44
(%)	41%	50%	91%	93%	100%	100%	93%	93%	23%	7%

Table 2: Patients receiving extra intravenous fluids.

Electrolyte values are listed in Table 3. IVF administration had a significant effect on creatinine and sodium levels. Mean creatinine pre-treatment was 0.86 (range 0.4-1.2) and post-treatment 0.77 (range 0.3-1.0) P<0.0001. Mean sodium pre-treatment was 137.8 (range 134-141) and post-treatment 136.5 (range 132-141) P<0.0002. BUN levels were lowered with IVF but not significantly. Mean BUN pre-treatment was 14.3 (range 6.0-22.0) and post-treatment 13.8 (range 5.0-24.0) p=0.30. Magnesium levels were slightly lower before and after treatment. Mean Mg pre-treatment was 2.0 (range 1.4-2.4) and post-treatment 1.92 (range 1.3-2.4) P=0.057. Potassium levels were slightly increased with IVF but also not significantly. Mean potassium pre-treatment was 4.21 (range 3.5-5.0) and post-treatment was 4.25 (range 3.0-4.9) P=0.36. Only five patients (11%) had grade 1 hypomagnesemia. No patients experienced renal toxicity of any grade.

Electrolytes	Mean	Standard Deviation	Minimum	Maximum	t Value	P value
BUN pre-treatment	14.36	3.82	6	22		
BUN post-treatment	13.77	4.36	5	24		
BUN delta	-0.59	3.74	-10	8	-1.05	0.3001
Creatinine pre-treatment	0.86	0.18	0.4	1.2		
Creatinine post-treatment	0.77	0.17	0.3	1		
Creatinine delta	-0.09	0.12	-0.4	0.2	-5.11	<0.0001
Na pre-treatment	137.86	2.27	134	141		
Na post-treatment	136.5	1.93	132	141		
Na delta	-1.36	2.19	-6	4	-4.13	0.0002
K pre-treatment	4.21	0.32	3.5	5		
K post-treatment	4.25	0.41	3	4.9		
K delta	0.04	0.29	-0.6	0.6	0.93	0.3566
Mg pre-treatment	2	0.19	1.4	2.4		
Mg post-treatment	1.92	0.27	1.3	2.4		
Mg Delta	-0.08	0.27	-0.6	0.6	-1.96	0.0571
Phos pre-treatment	3.55	0.41	2.7	4.8		
Phos post-treatment	3.45	0.67	1.5	4.5		
Phos Delta	-0.1	0.78	-2.5	1.4	-0.85	0.3982

Table 3: Electrolytes before and after treatment.

The hematologic toxicity was manageable with cisplatin dose adjustments. Ten patients (23%) experienced grade 1 neutropenia, and five patients (11%) experienced grade II neutropenia. Five patients (11%) experienced grade II thrombocytopenia. Cisplatin dose reductions were used in all patients with grade II neutropenia and/or thrombocytopenia. Ten patients (23%) experienced grade 1 anemia and 4 patients (9%) experienced grade II anemia. No transfusions were necessary in any case for symptomatic management.

Three patients (7%) receiving definitive CRT were admitted to the hospital during the last week of treatment due to aspiration pneumonia. All patients were discharged within 72 h with oral antibiotics. Only two patients (4.5%) were still PEG-tube dependent at six months of treatment completion. No treatment related deaths were observed.

The overall median follow-up was 19 months, with 9 patients having relapsed. Progression free survival rate at 1 and 2 years were 84.1% and 77.1%, respectively (Figure 1). In patients who progressed, the median time to progression was 5 months. The one year survival rate was 90.7% (Figure 2). Of the 9 patients who relapsed, 4 had died due to progression of their disease.

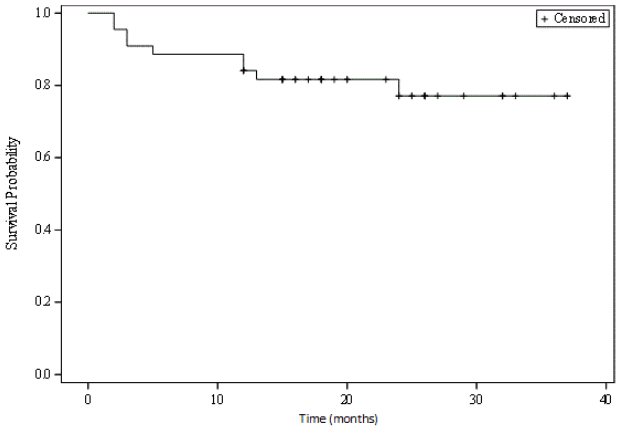

Figure 1: Progression free survival.

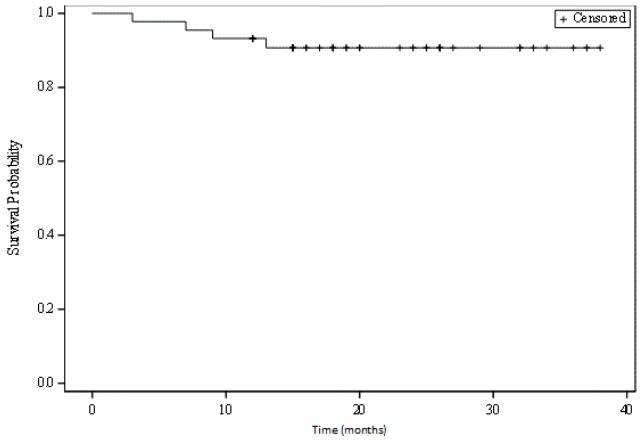

Figure 2: Overall survival.

Discussion

The best way to assess early signs of dehydration in any given clinical setting remains a controversial issue. Uosm and USG are less invasive when compared to Posm and USG has been found to be an inexpensive, simple, fast, and accurate indicator of hydration status [6,10]. Testing USG has been shown to be a reliable and an important indicator of the body absolute hydration status that can be used as a single measurement in industrial workers under thermal stress working extended shifts [11]. Furthermore, USG has been shown to be a sensitive marker for dehydration among athletes [12]. The American College of Sports Medicine has established categories of hydration status based on USG measurements, with USG 1.000-1.019 representing euhydration, 1.020-1.024 representing slight dehydration and ≥ 1.025 representing significant dehydration [13]. Early detection of dehydration and its prevention with fluid replacement seems to reduce the risk of cisplatin-related renal toxicity [4]. In head and neck cancer patients receiving CRT, the risk of dehydration related to decreased oral intake appears to be a common finding [7]. To our knowledge, there is no data on the use of USG for dehydration management of head and neck cancer patients. We used these guidelines as a framework for our hydration algorithm.

This single-arm experience found that serial measurements of USG was a feasible method for assessing hydration status and initiating IV fluid supportive care during administration of cisplatin-based CRT to head and neck cancer patients. All patients in this cohort maintained good renal function as evidenced by normal creatinine clearance throughout their treatments.

There were several limitations to this study. Most notably, as a single-arm study we could not directly compare whether the hydration algorithm led to a risk reduction in nephrotoxicity. And while indirect comparison of our findings shows a large risk reduction as compared to historical data of patients on CRT, this difference may have been due to other measures. In particular, all patients in this study underwent placement of a prophylactic PEG-tube to reduce the risk of dehydration, malnutrition, and weight loss. Unfortunately, there is no reliable data regarding the impact of prophylactic feeding tube placement on the rate of renal toxicity in patients receiving definitive RT or concomitant CRT but the risk of hospital admissions is still high [14]. On a retrospective study of 88 patients with locally advanced head and neck cancer undergoing concurrent CRT, prophylactic G-tubes were associated with fewer hospitalizations for nutritional or dehydration issues (34% vs. 13%, p=0.04), maintenance of weight, and fewer treatment interruptions (18% vs. 0%, p=0.08) [15]. Current guidelines recommend strong consideration of prophylactic placement for "high-risk" patients. Per NCCN guidelines [16], this includes patients with severe pre-treatment weight loss, on-going dehydration or dysphagia, significant comorbidities, severe aspiration, and anticipated swallowing issues. The high risk of dysphagia with CRT was the basis for prophylactic G-tube placement in our patient population.

In terms of applicability, the findings from this study can still be utilized because even with the wider use of prophylactic PEG-tubes, head and neck cancer patients remain at risk for dehydration and hospitalization during CRT. Although the rate was significantly less than patients who did not have prophylactic PEG tubes, a recent study found that 33% of prophylactic G-tube patients still required hospitalization at some point during CRT for dehydration, malnutrition, dysphagia or G-tube-related problems [17].

Furthermore, some patients refuse G-tube placement due to personal preference and so remain at substantially higher risk for dehydration.

In conclusion, head and neck cancer patients who are treated with CRT are at high risk for dehydration due to mucositis, nausea and vomiting. Dehydration can put patients at further risk for cisplatin nephrotoxicity, unplanned hospitalizations, treatment delays and worse outcomes. The absence of nephrotoxicity in this study is promising and warrants further investigation as to whether the implementation of this USG algorithm for fluid replacement can reduce the risk of nephrotoxicity and remain cost-effective.

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